```
Set      Items   Description
S1        5076   TNF AND AUTOIMMUN?
S2         517   S1 AND REVIEW?
S3          38   S2 AND (CORRELAT? OR PREDICT? OR DIFFICULT?)
S4          28   RD S3 (unique items)
S5        2273   (TNF?)(10N)(ANTIBOD?)(20N)(TREAT? OR THERAP? OR ADMINIST? -
             OR INHIBIT? OR SUPPRESS? OR PREVENT?)(30N)(INFLAMM? OR AUTOIM-
             MUN?)
S6         406   (TNF?)(10N)(ANTIBOD?)(20N)(TREAT? OR THERAP? OR ADMINIST? -
             OR INHIBIT? OR SUPPRESS? OR PREVENT?)(30N)(INFLAMM? OR AUTOIM-
             MUN?)(20N)(CORRELAT? OR PREDICT? OR LACK OR FAIL?)
S7         180   RD S6 (unique items)
S8        2035   METHOTREXATE(20N)(AUTOIMMUN? OR INFLAMM?)
S9         318   METHOTREXATE(20N)(AUTOIMMUN? OR INFLAMM?) AND REVIEW?
S10         39   S9 AND AUTOIMMUN?
S11         31   RD S10 (unique items)
S12       1221   METHOTREXATE AND TNF?
S13         43   S12 AND PY<1993
S14         26   RD S13 (unique items)
S15       4862   METHOTREXATE (10N)(ARTHRITIS OR AUTOIMMUN?)
S16       1440   S15 AND PY<1993
S17         42   S16 AND AUTOIMMUN?
S18         33   RD S17 (unique items)
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Set      Items    Description
S1        5076    TNF AND AUTOIMMUN?
S2         517    S1 AND REVIEW?
S3          38    S2 AND (CORRELAT? OR PREDICT? OR DIFFICULT?)
S4          28    RD S3 (unique items)
S5        2273    (TNF?)(10N)(ANTIBOD?)(20N)(TREAT? OR THERAP? OR ADMINIST? -
             OR INHIBIT? OR SUPPRESS? OR PREVENT?)(30N)(INFLAMM? OR AUTOIM-
             MUN?)
S6         406    (TNF?)(10N)(ANTIBOD?)(20N)(TREAT? OR THERAP? OR ADMINIST? -
             OR INHIBIT? OR SUPPRESS? OR PREVENT?)(30N)(INFLAMM? OR AUTOIM-
             MUN?)(20N)(CORRELAT? OR PREDICT? OR LACK OR FAIL?)
S7         180    RD S6 (unique items)
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Set      Items    Description
S1        5076    TNF AND AUTOIMMUN?
S2         517    S1 AND REVIEW?
S3          38    S2 AND (CORRELAT? OR PREDICT? OR DIFFICULT?)
S4          28    RD S3 (unique items)
S5        2273    (TNF?)(10N)(ANTIBOD?)(20N)(TREAT? OR THERAP? OR ADMINIST? -
              OR INHIBIT? OR SUPPRESS? OR PREVENT?)(30N)(INFLAMM? OR AUTOIM-
              MUN?)
S6         406    (TNF?)(10N)(ANTIBOD?)(20N)(TREAT? OR THERAP? OR ADMINIST? -
              OR INHIBIT? OR SUPPRESS? OR PREVENT?)(30N)(INFLAMM? OR AUTOIM-
              MUN?)(20N)(CORRELAT? OR PREDICT? OR LACK OR FAIL?)
S7         180    RD S6 (unique items)
S8        2035    METHOTREXATE(20N)(AUTOIMMUN? OR INFLAMM?)
S9         318    METHOTREXATE(20N)(AUTOIMMUN? OR INFLAMM?) AND REVIEW?
S10         39    S9 AND AUTOIMMUN?
S11         31    RD S10 (unique items)
S12       1221    METHOTREXATE AND TNF?
S13         43    S12 AND PY<1993
S14         26    RD S13 (unique items)
?
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**Gambel, Phillip**

**To:** STIC-ILL
**Subject:** feldmann amd

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please provide the following to

phillip gambel
ar tunit 1644
272-0844

1644 mailbox 3c70

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6/7/7 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE


05215370 EMBASE No: 1992355604
Use of monoclonal antibodies in vivo as a therapeutic strategy for alloimmune or autoimmune reactivity: The Besancon experience
Herve P.; Racadot E.; Wendling D.; Rumbach L.; Tiberghien P.; Cahn J.Y.; Flesch M.; Wijdenes J.
Centre Reg. de Transfusion Sanguine, 1 Boulevard Fleming,25020 Besancon France
Immunological Reviews ( IMMUNOL. REV. ) (Denmark) 1992, -/129 (31-55)
CODEN: IMRED ISSN: 0105-2896
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH

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6/7/8 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)


07817709 93273249 PMID: 8388844
Rheumatoid arthritis: new science, new treatment.
Miller-Blair D J; Robbins D L
Kaiser-Permanente Medical Center, South Sacramento, CA.
Geriatrics (UNITED STATES) Jun 1993, 48 (6) p28-31, 35-8,
ISSN 0016-867X Journal Code: 2985102R
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that occurs two to four times as often in women as in men and increases in incidence with advancing age. It affects synovial-lined joints and can also affect the pulmonary, cardiac, nervous, integumentary, and reticuloendothelial systems. RA is manifested clinically by malaise and fatigue, followed by a symmetric pattern of joint inflammation characterized by pain and stiffness. RA most likely occurs in the setting of a genetically predisposed individual, triggered by infectious agents or endogenous antigens. Many of the newer treatments being studied involve

blocking cytokine-mediated interactions between cells of the synovium. (18 Refs.)
Record Date Created: 19930629
Record Date Completed: 19930629

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6/7/9 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2004 The Dialog Corp. All rts. reserv.

07764235 93219728 PMID: 8465132
[If I had chronic polyarthritis--current ideas on basic therapy]
Wenn ich eine chronische Polyarthritis hatte--Neue Ideen zur Basistherapie.
Hasler F
FMH Innere Medizin, speziell Rheumaerkrankungen, Chur.
Schweizerische Rundschau fur Medizin Praxis = Revue suisse de medecine Praxis (SWITZERLAND) Mar 23 1993, 82 (12) p349-52, ISSN 1013-2058 Journal Code: 8403202
Document type: Journal Article ; English Abstract
Languages: GERMAN
Main Citation Owner: NLM
Record type: Completed
Rheumatoid arthritis (RA) is a chronic inflammatory disorder of largely unknown etiology and complex multifactorial pathogenesis. To date, the medical management has been less than optimal and has consisted primarily of drugs that modulate the acute inflammatory process. Over the years a treatment program referred to as the classical therapeutic pyramid has evolved. A new concept and a controversial one in therapy of RA is that already at the time of definitive diagnosis, a more concerted effort towards vigorous treatment using second-line drugs such as methotrexate , should be made. It is very likely that over the next 5 years interventions such as monoclonal antibodies directed against predetermined T-cell subpopulations and anti-cytokines such as TNF -alpha binding proteins will evolve as new concepts in therapy of RA.
Record Date Created: 19930506
Record Date Completed: 19930506

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6/7/10 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2004 The Dialog Corp. All rts. reserv.

06917860 91158187 PMID: 2001072
Increased TNF-alpha secretion by alveolar macrophages from patients with rheumatoid arthritis.
Gosset P; Perez T; Lassalle P; Duquesnoy B; Farre J M; Tonnel A B; Capron A
Centre d'Immunologie et de Biologie Parasitaire, Unite mixte INSERM, CNRS, Lille, France.
American review of respiratory disease (UNITED STATES) Mar 1991, 143 (3) p593-7, ISSN 0003-0805 Journal Code: 0370523
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Tumor necrosis factor alpha (TNF) and interleukin-1 (IL-1) production by alveolar macrophages (AM) was evaluated in 17 rheumatoid arthritis (RA) patients without interstitial lung disease (ILD, Group 1) and 14 RA patients with clinical ILD (Group 2) in comparison with 10 control

subjects. AM after recovery by bronchoalveolar lavage were selected by adherence, and then supernatants were collected after 3 or 24 h of culture. Results showed no modification of IL-1 synthesis in either group of RA patients. Spontaneous TNF production was significantly increased in Group 2 (2.5 +/- 0.5 ng/ml) as well as in Group 1 (2.4 +/- 0.4 ng/ml) compared with control subjects (0.43 +/- 0.1 ng/ml, p less than 0.001). In addition, AM from patients untreated or treated exclusively by nonsteroidal antiinflammatory drugs produced similar levels of TNF, whereas those receiving corticosteroids, second-line drugs (such as sulfasalazine, aurothiomalate, and methotrexate), or the combination of both therapy regimens released significantly less TNF. Interestingly, TNF was not different in both groups, but Group 2 had a markedly increased ratio of local immune complex to albumin in bronchoalveolar lavage fluid (0.47 +/- 0.12 versus 0.07 +/- 0.02 in Group 1; p less than 0.002). TNF thus appears an additional component of RA subclinical alveolitis in RA, but its prognostic value and its precise role in lung damage remain to be determined. Development of ILD requires certainly complex interactions of synergistic factors, possibly including local immune complexes detected in BAL fluids.
Record Date Created: 19910410
Record Date Completed: 19910410

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6/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


0009020892 BIOSIS NO.: 199497042177
Elevated levels of TNF in the joints of adjuvant arthritic rats
AUTHOR: Smith-Oliver Tracey; Noel L Staton; Stimpson Steven S; Yarnall David P; Connolly Kevin M (Reprint)
AUTHOR ADDRESS: Dep. Immunology, Glaxo Res. Inst., Five Moore Drive, Research Triangle Park, NC 27709, USA**USA
JOURNAL: Cytokine 5 (4): p298-304 1993 1993
ISSN: 1043-4666
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The primary purpose of this study was to determine whether local levels of tumor necrosis factor (TNF) were elevated in chronically inflamed joints in rats with adjuvant-induced arthritis (AA). We also wished to develop methodology for the quantitative measurement of joint TNF, and to examine the effects of known anti-inflammatory agents on joint TNF levels. TNF levels were measured in joints from AA rats taken during the systemic phase (day 20) of arthritic disease. Using the L929 bioassay, joint extracts from AA rats had significantly greater TNF levels (1054 +- 147 pg/g tissue) than joint extracts from normal rats (110 +- 42 pg/g tissue). Administration of ibuprofen failed to significantly inhibit TNF levels in the joint at a time point when paw swelling was significantly reduced. The immunomodulating agents, methotrexate, cyclosporin A (CSA) and HWA486 profoundly inhibited both joint TNF levels and paw swelling. The specificity of this assay for TNF was supported by studies with a polyclonal rabbit anti-mouse TNF antibody which neutralized 78-87% of the TNF activity in the joint extracts. Our studies demonstrate a quantitative increase in local TNF expression in adjuvant arthritis and support a role for TNF in chronic inflammation.

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7/1 (Item 1 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)
(c) 2004 BIOSIS. All rts. reserv.

0012861593 BIOSIS NO.: 200100033432
Infliximab and methotrexate in the treatment of rheumatoid arthritis
AUTHOR: Lipsky Peter E (Reprint); Van Der Heijde Desiree M F M; St Clair E William; Furst Daniel E; Breedveld Ferdinand C; Kalden Joachim R; Smolen Josef S; Weisman Michael; Emery Paul; Feldmann Marc; Harriman Gregory R; Maini Ravinder N
AUTHOR ADDRESS: National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, 9000 Rockville Pike, Bldg. 10, Rm. 9N228, Bethesda, MD, 20892-1820, USA**USA
JOURNAL: New England Journal of Medicine 343 (22): p1594-1602 November 30, 2000 2000
MEDIUM: print
ISSN: 0028-4793
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background Neutralization of tumor necrosis factor alpha ( TNF-alpha) for three to six months reduces the symptoms and signs of rheumatoid arthritis. However, the capacity of this approach to effect a more sustained benefit and its effect on joint damage are not known. Methods We treated 428 patients who had active rheumatoid arthritis despite methotrexate therapy with placebo or infliximab, a chimeric monoclonal antibody against TNF-alpha, in intravenous doses of 3 or 10 mg per kilogram of body weight every 4 or 8 weeks in combination with oral methotrexate for 54 weeks. We assessed clinical responses with use of the criteria of the American College of Rheumatology, the quality of life with a health-status questionnaire, and the effect on joint damage radiographically. Results The combination of infliximab and methotrexate was well tolerated and resulted in a sustained reduction in the symptoms and signs of rheumatoid arthritis that was significantly greater than the reduction associated with methotrexate therapy alone (clinical response, 51.8 percent vs. 17.0 percent; P<0.001). The quality of life was also significantly better with infliximab plus methotrexate than with methotrexate alone. Radiographic evidence of joint damage increased in the group given methotrexate, but not in the groups given infliximab and methotrexate (mean change in radiographic score, 7.0 vs. 0.6; P<0.001). Radiographic evidence of progression of joint damage was absent in infliximab-treated patients whether or not they had a clinical response. Conclusions In patients with persistently active rheumatoid arthritis despite methotrexate therapy, repeated doses of infliximab in combination with methotrexate provided clinical benefit and halted the progression of joint damage.

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11/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0012391326 BIOSIS NO.: 200000109639
Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: A randomised phase III trial
AUTHOR: Maini Ravinder (Reprint); St Clair E William; Breedveld Ferdinand; Furst Daniel; Kalden Joachim; Weisman Michael; Smolen Josef; Emery Paul; Harriman Gregory; Feldmann Marc; Lipsky Peter
AUTHOR ADDRESS: The Kennedy Institute of Rheumatology and The Imperial College School of Medicine at Charing Cross Hospital, London, W6 8LH, UK **UK

JOURNAL: Lancet (North American Edition) 354 (9194): p1932-1939 Dec. 4, 1999 1999
MEDIUM: print
ISSN: 0099-5355
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background Not all patients with rheumatoid arthritis can tolerate or respond to methotrexate, a standard treatment for this disease. There is evidence that antitumor necrosis factor alpha ( TNFalpha) is efficacious in relief of signs and symptoms. We therefore investigated whether infliximab, a chimeric human-mouse anti-TNFalpha monoclonal antibody would provide additional clinical benefit to patients who had active rheumatoid arthritis despite receiving methotrexate. Methods In an international double-blind placebo-controlled phase III clinical trial, 428 patients who had active rheumatoid arthritis, who had received continous methotrexate for at least 3 months and at a stable dose for at least 4 weeks, were randomised to placebo (n=88) or one of four regimens of infliximab at weeks 0, 2, and 6. Additional infusions of the same dose were given every 4 or 8 weeks thereafter on a background of a stable dose of methotrexate (median 15 mg/week for gtoreq6 months, range 10-35 mg/wk). Patients were assessed every 4 weeks for 30 weeks. Findings At 30 weeks, the American College of Rheumatology (20) response criteria, representing a 20% improvement from baseline, were achieved in 53, 50, 58, and 52% of patients receiving 3 mg/kg every 4 or 8 weeks or 10 mg/kg every 4 or 8 weeks, respectively, compared with 20% of patients receiving placebo plus methotrexate ($p<0.001$ for each of the four infliximab regimens vs placebo). A 50% improvement was achieved in 29, 27, 26, and 31% of infliximab plus methotrexate in the same treatment groups, compared with 5% of patients on placebo plus methotrexate ($p<0.001$). Infliximab was well-tolerated; withdrawals for adverse events as well as the occurrence of serious adverse events or serious infections did not exceed those in the placebo group. Interpretation During 30 weeks, treatment with infliximab plus methotrexate was more efficacious than methotrexate alone in patients with active rheumatoid arthritis not previously responding to methotrexate.

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13/7/27 (Item 14 from file: 73)
DIALOG(R)File 73:EMBASE


05657234 EMBASE No: 1994070548
Novel immunosuppressive and antiinflammatory drugs: A 1993 perspective
Allison A.C.
Dawa Corporation,Belmont, CA United States
Annals of the New York Academy of Sciences ( ANN. NEW YORK ACAD. SCI. ) ( United States) 1993, 696/- (XI-XX)
CODEN: ANYAA ISSN: 0077-8923
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Research on immunosuppressive and antiinflammatory drugs is progressing rapidly. Several new drugs are in development, and learning how to combine them optimally, for treatment of different diseases and prolonging graft survival, will be a major task for the next few years. Decreasing the incidence of complications following transplantation will reduce patient anxiety and cost, and the shortage of donor organs is an additional reason for wishing to prolong graft acceptance. Many clinical findings with the new drug combinations should be published by the end of the century. We can

begin the next millennium with improved immunosuppressive and antiinflammatory drugs discussed at the Orlando conference.

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0007390929  BIOSIS NO.: 199140033820
METHOTREXATE MECHANISM OF ACTION IN RHEUMATOID ARTHRITIS
AUTHOR: SEGAL R (Reprint); YARON M; TARTAKOVSKY B
AUTHOR ADDRESS: DEP RHEUMATOLOGY, ICHILOV HOSP, TEL-AVIV 64239, ISRAEL**
ISRAEL
JOURNAL: Seminars in Arthritis and Rheumatism 20 (3): p190-200 1990
ISSN: 0049-0172
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: ENGLISH

13/7/12  (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0006488745  BIOSIS NO.: 198937066494
EFFECTS OF TUMOR NECROSIS FACTOR AND COMBINATION CYCLOSPORIN A-METHOTREXATE THERAPY ON COLLAGEN ARTHRITIS
AUTHOR: BRAHN E (Reprint); BANQUERIGO M L C; LIU D Y
AUTHOR ADDRESS: UCLA SCH MED, LOS ANGELES, CALIF 90024, USA**USA
JOURNAL: Arthritis and Rheumatism 32 (4 SUPPL): pS133 1989
CONFERENCE/MEETING: 53RD ANNUAL SCIENTIFIC MEETING OF THE AMERICAN COLLEGE OF RHEUMATOLOGY, CINCINNATI, OHIO, USA, JUNE 12-17, 1989. ARTHRITIS RHEUM.
ISSN: 0004-3591
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH

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0007747592  BIOSIS NO.: 199191130483
INCREASED TNF-ALPHA SECRETION BY ALVEOLAR MACROPHAGES FROM PATIENTS WITH RHEUMATOID ARTHRITIS
AUTHOR: GOSSET P (Reprint); PEREZ T; LASSALLE P; DUQUESNOY B; FARRE J M; TONNEL A B; CAPRON A
AUTHOR ADDRESS: CENTRE IMMUNOLOGIE BIOLOGIE PARASITAIRE, UNITE MIXTE INSERM 167, CNRS 624, BP 245, INSTITUT PASTEUR, 59019 LILLE CEDEX, FR**FRANCE
JOURNAL: American Review of Respiratory Disease 143 (3): p593-597
1991
ISSN: 0003-0805
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Tumor necrosis factor .alpha. (TNF) and interleukin-1 (IL-1) production by alveolar macrophages (AM) was evaluated in 17 rheumatoid arthritis (RA) patients without interstitial disease (ILD, Group 1) and 14 RA patients with clinical ILD (Group 2) in comparison with 10 control subjects. AM after recovery by bronchoalveolar lavage were selected by adherence, and then supernatants were collected after 3 or 24 h of culture. Results showed no modification of IL-1 synthesis in either group of RA patients. Spontaneous TNF production was significantly increased in Group 2 (2.5 .+-. 0.5 ng/ml) as well as in Group 1 (2.4 .+-. 0.4 ng/ml) compared with control subjects (0.43 .+-. 0.1 ng/ml, $p < 0.001$). In addition, AM from patients untreated or treated exclusively by nonsteroidal antiinflammatory drugs produced

similar levels of TNF, whereas those receiving corticosteroids, second-line drugs (such as sulfasalzine, aurothiomalate, and methotrexate), or the combination of both therapy regimens released significantly less TNF. Interestingly, TNF was not different in both groups, but Group 2 had a markedly increased ratio of local immune complex to albumin in bronchoalveolar lavage fluid (0.47 .+-. 0.12 versus 0.07 .+-. 0.02 in Group 1; $p < 0.002$). TNF thus appears an additional component of RA subclinical alveolitis in RA, but its prognostic value and its precise role in lung damage remain to be determined. Development of ILD requires certainly complex interactions of synergistic factors, possibly including local immune complexes detected in BAL fluids.

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0009614371  BIOSIS NO.: 199598082204
Circulating concentrations and production of cytokines and soluble receptors in rheumatoid arthritis patients: Effects of a single dose methotrexate
AUTHOR: Barrera P (Reprint); Boerbooms A M T; Demacker P N M; Van De Putte L B A; Gallati H; Van Der Meer J W M
AUTHOR ADDRESS: Dep. Rheumatol., Univ. Hosp., Nijmegen, Netherlands** Netherlands
JOURNAL: British Journal of Rheumatology 33 (11): p1017-1024 1994
1994
ISSN: 0263-7103
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Methotrexate (MTX) is an effective treatment for RA and its effects may be partly due to cytokine modulation. Herein, we assessed the effects of a single MTX dose on the production and circulating concentrations of several cytokines and soluble receptors in 42 RA patients on three consecutive days. Three patient groups were studied: (a) 16 patients taking the first MTX dose, (b) 11 patients on chronic MTX treatment and (c) a control group of 15 patients not treated with MTX. Cytokine production was studied in peripheral blood mononuclear cells (PBMNC) and in a whole-blood culture system (WBCS). Group (a) had a more active disease according to laboratory parameters as well as higher circulating IL-6 levels ($P = 0.002$). The secretion of IL-1-beta by stimulated PBMNC ($P = 0.008$) was higher in this group and decreased significantly ($P = 0.03$) after a single MTX dose. No significant change in any parameter was observed after MTX in group (b). In the total patient group, circulating concentrations of IL-1-beta and TNF -alpha were low but blood cells showed a high capacity of production for these cytokines. In contrast for sTNFRs, high circulating levels but a limited in vitro production were observed. In conclusion, a single MTX dose may result in decreased production of IL-1-beta by PBMNC in patients with active RA. Furthermore, we observed an imbalance in the production of TNF-alpha and sTNFRs by peripheral blood cells of RA patients and propose that the WBCS is convenient for studying cytokine production in RA.

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13/7/5  (Item 5 from file: 5)
DIALOG(R)File  5:Biosis Previews(R)


0008935483  BIOSIS NO.: 199396099899
Circulating soluble tumor necrosis factor receptors,

interleukin-2 receptors, tumor necrosis factor alpha, and interleukin-6 levels in rheumatoid arthritis: Longitudinal evaluation during methotrexate and azathioprine therapy
AUTHOR: Barrera Pilar (Reprint); Boerbooms Agnes M T; Janssen Elly M; Sauerwein Robert W; Gallati H; Mulder Jan; De Boo Theo; Demacker Pierre N M; Van Der Putte Levinus B A; Van Der Meer Jos W M
AUTHOR ADDRESS: Dep. Rheumatol. Internal Med., Univ. Hosp. Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, Netherlands**Netherlands
JOURNAL: Arthritis and Rheumatism 36 (8): p1070-1079 1993
ISSN: 0004-3591
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Objective. To assess whether circulating concentrations of soluble tumor necrosis factor receptors (sTNFR; p55 and p75), soluble interleukin-2 receptors (sIL-2R), tumor necrosis factor a (TNF-alpha), and interleukin-6 (IL-6) reflect clinical response and whether changes are dependent on the drug used in rheumatoid arthritis (RA) patients taking methotrexate (MTX) or azathioprine (AZA). were assessed in 20 control subjects and serially for up to 48 weeks in 61 RA patients, by bioassay (IL-6) and immunoassays (sTNFR, sIL-2R, TNF-alpha, and IL-6). Results. Concentrations of p55 and p75, sIL-2R, and TNF-alpha (but not IL-6) were significantly higher in RA patients than in controls. Significant decreases in sIL-2R and p55 concentrations were associated with clinical improvement and were observed in patients treated with, MTX, but not AZA. Both treatments induced decreases in IL-6 concentrations, but circulating AZA (or its metabolites) appears to interfere with the measurement of IL-6 bioactivity. TNF-alpha and p75 levels did not show significant changes. Conclusion. Measurement of circulating sIL-2R, p55, and IL-6 may be useful in the evaluation of RA disease activity and response to therapy. Interference by circulating levels of drugs must be ruled out when bioassays are used to evaluate cytokine levels.

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16/7/16 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)


06917860 91158187 PMID: 2001072
Increased TNF-alpha secretion by alveolar macrophages from patients with rheumatoid arthritis.
Gosset P; Perez T; Lassalle P; Duquesnoy B; Farre J M; Tonnel A B; Capron A
Centre d'Immunologie et de Biologie Parasitaire, Unite mixte INSERM, CNRS, Lille, France.
American review of respiratory disease (UNITED STATES) Mar 1991, 143 (3) p593-7, ISSN 0003-0805 Journal Code: 0370523
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Tumor necrosis factor alpha (TNF) and interleukin-1 (IL-1) production by alveolar macrophages (AM) was evaluated in 17 rheumatoid arthritis (RA) patients without interstitial lung disease (ILD, Group 1) and 14 RA patients with clinical ILD (Group 2) in comparison with 10 control subjects. AM after recovery by bronchoalveolar lavage were selected by adherence, and then supernatants were collected after 3 or 24 h of culture. Results showed no modification of IL-1 synthesis in either group of RA patients. Spontaneous TNF production was significantly increased in Group 2 (2.5 +/- 0.5 ng/ml) as well as in Group 1 (2.4 +/- 0.4 ng/ml) compared with

control subjects (0.43 +/- 0.1 ng/ml, p less than 0.001). In addition, AM from patients untreated or treated exclusively by nonsteroidal antiinflammatory drugs produced similar levels of TNF, whereas those receiving corticosteroids, second-line drugs (such as sulfasalazine, aurothiomalate, and methotrexate), or the combination of both therapy regimens released significantly less TNF. Interestingly, TNF was not different in both groups, but Group 2 had a markedly increased ratio of local immune complex to albumin in bronchoalveolar lavage fluid (0.47 +/- 0.12 versus 0.07 +/- 0.02 in Group 1; p less than 0.002). TNF thus appears an additional component of RA subclinical alveolitis in RA, but its prognostic value and its precise role in lung damage remain to be determined. Development of ILD requires certainly complex interactions of synergistic factors, possibly including local immune complexes detected in BAL fluids.
Record Date Created: 19910410

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16/7/13 (Item 13 from file: 73)
DIALOG(R)File 73:EMBASE


04180294 EMBASE No: 1990062836
Design of combination biotherapy studies: future goals and challenges
Gilewski T.A.; Golomb H.M.
Section of Hematology/Oncology, University of Chicago Medical Center, 5841 S Maryland Avenue, Box 420, Chicago, IL 60637 United States
Seminars in Oncology ( SEMIN. ONCOL. ) (United States) 1990, 17/1 SUPPL. 1 (3-10)
CODEN: SOLGA ISSN: 0093-7754
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The recent large-scale production of biomodulators, also known as biologic response modifiers, made possible through recombinant DNA technology, offers the potential for significant advances in the treatment of cancer. The antitumor activity of these agents, such as interferons, interleukins, and tumor necrosis factor, have generated enthusiasm for further investigation. In an effort to improve response rates, combinations of these agents both with and without conventional therapies are currently being examined. Clinical trials have been conducted with various therapeutic combinations, including a biomodulator plus chemotherapy, combinations of different biomodulators, a biomodulator with concomitant chemotherapy and radiation, and multiple combinations of chemotherapies and biomodulators. These approaches are promising and some limited successes have been reported; however, the goal of increased anticancer activity without greater toxicities or antagonism between various agents is not always achieved. Synergism among active agents is not necessarily assured and quite unexpected and unpredictable toxicities have been noted. The studies to date suggest that important new therapies will emerge, but many questions have to be answered before the specific roles of these new treatments are defined.

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et     Items   Description
S1      2871   (TNF? OR TUMOR(W)NECROSIS OR TUMOUR(W)NECROSIS) AND METHOT-
           REXATE
S2      1727   S1 AND (AUTOIMMUN? OR ARTHRITIS)
S3      1077   (TNF? OR TUMOR(W)NECROSIS OR TUMOUR(W)NECROSIS)(20N)(ANTIB-
           OD?) AND METHOTREXATE
S4       754   S3 AND (ARTHRITIS OR AUTOIMMUN?)
S5        12   S4 AND PY<1995
S6        10   RD S5 (unique items)
S7       161   E1-E2
S8        97   S7 AND TNF?
S9        91   RD S8 (unique items)
S10        2   S9 AND METHOTREXATE
S11        2   RD S10 (unique items)
S12       72   S2 AND PY<1995
S13       54   RD S12 (unique items)
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 and (combination or combine? or synerg? or together)
Processing
          166065  TNF?
         2016475  TUMOR
          480565  NECROSIS
          258617  TUMOR(W)NECROSIS
          214751  TUMOUR
          480565  NECROSIS
           23815  TUMOUR(W)NECROSIS
         1865219  ANTIBOD?
           25808  ((TNF? OR TUMOR(W)NECROSIS) OR
                  TUMOUR(W)NECROSIS)(20N)ANTIBOD?
          121697  METHOTREXATE
         1071821  COMBINATION
          887186  COMBINE?
          209998  SYNERG?
          546574  TOGETHER
     S14     584  (TNF? OR TUMOR(W)NECROSIS OR
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                  (COMBINATION OR COMBINE? OR SYNERG? OR TOGETHER)
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Processing
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        36149661  PY<1995
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...completed examining records
     S16     16   RD S15 (unique items)
? t s16/7/all

 16/7/1     (Item 1 from file: 73)
DIALOG(R)File  73:EMBASE
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OS  - DIALOG OneSearch
  File   5:Biosis Previews(R)  1969-2004/Feb W1
         (c) 2004 BIOSIS
  File  73:EMBASE  1974-2004/Feb W1
         (c) 2004 Elsevier Science B.V.
  File 155:MEDLINE(R)  1966-2004/Feb W1
         (c) format only 2004 The Dialog Corp.
*File 155: Medline is updating again (12-22-2003).
Please see HELP NEWS 154, for details.
  File 399:CA SEARCH(R)  1967-2004/UD=14006
         (c) 2004 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement.
Alert feature enhanced for multiple files, etc. See HELP ALERT.

      Set  Items  Description
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          480565  NECROSIS
          258617  TUMOR(W)NECROSIS
          214751  TUMOUR
          480565  NECROSIS
           23815  TUMOUR(W)NECROSIS
          121697  METHOTREXATE
      S1    2871  (TNF? OR TUMOR(W)NECROSIS OR TUMOUR(W)NECROSIS) AND
                  METHOTREXATE
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           2871  S1
         215860  AUTOIMMUN?
         374079  ARTHRITIS
      S2    1727  S1 AND (AUTOIMMUN? OR ARTHRITIS)
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         2016475  TUMOR
          480565  NECROSIS
          258617  TUMOR(W)NECROSIS
          214751  TUMOUR
          480565  NECROSIS
           23815  TUMOUR(W)NECROSIS
         1865219  ANTIBOD?
           25808  ((TNF? OR TUMOR(W)NECROSIS) OR
                  TUMOUR(W)NECROSIS)(20N)ANTIBOD?
          121697  METHOTREXATE
      S3    1077  (TNF? OR TUMOR(W)NECROSIS OR
                  TUMOUR(W)NECROSIS)(20N)(ANTIBOD?) AND METHOTREXATE
? s s3 and (arthritis or autoimmun?)
           1077  S3
         374079  ARTHRITIS
         215860  AUTOIMMUN?
      S4    754  S3 AND (ARTHRITIS OR AUTOIMMUN?)
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Processing
Processing
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       36149661  PY<1995
      S5     12  S4 AND PY<1995
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...completed examining records
      S6     10  RD S5 (unique items)
? t s6/7/all

 6/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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0009020892 BIOSIS NO.: 199497042177
Elevated levels of TNF in the joints of adjuvant arthritic rats
AUTHOR: Smith-Oliver Tracey; Noel L Staton; Stimpson Steven S; Yarnall David P; Connolly Kevin M (Reprint)
AUTHOR ADDRESS: Dep. Immunology, Glaxo Res. Inst., Five Moore Drive, Research Triangle Park, NC 27709, USA**USA
JOURNAL: Cytokine 5 (4): p298-304 1993 **1993**
ISSN: 1043-4666
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The primary purpose of this study was to determine whether local levels of tumor necrosis factor (TNF) were elevated in chronically inflamed joints in rats with adjuvant-induced **arthritis** (AA). We also wished to develop methodology for the quantitative measurement of joint TNF, and to examine the effects of known anti-inflammatory agents on joint TNF levels. TNF levels were measured in joints from AA rats taken during the systemic phase (day 20) of arthritic disease. Using the L929 bioassay, joint extracts from AA rats had significantly greater TNF levels (1054 +- 147 pg/g tissue) than joint extracts from normal rats (110 +- 42 pg/g tissue). Administration of ibuprofen failed to significantly inhibit TNF levels in the joint at a time point when paw swelling was significantly reduced. The immunomodulating agents, **methotrexate**, cyclosporin A (CSA) and HWA486 profoundly inhibited both joint TNF levels and paw swelling. The specificity of this assay for **TNF** was supported by studies with a polyclonal rabbit anti-mouse **TNF antibody** which neutralized 78-87% of the **TNF** activity in the joint extracts. Our studies demonstrate a quantitative increase in local **TNF** expression in adjuvant **arthritis** and support a role for TNF in chronic inflammation.

6/7/2 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE


05841072 EMBASE No: 1994253153
Pediatric rheumatic diseases
Warren R.W.; Perez M.D.; Wilking A.P.; Myones B.L.
Department of Pediatrics, Baylor College of Medicine, One Baylor Plaza,Houston, TX 77030 United States
Pediatric Clinics of North America ( PEDIATR. CLIN. NORTH AM. ) (United States) 1994, 41/4 (783-818)
CODEN: PCNAA ISSN: 0031-3955
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The rheumatic diseases of childhood are a relatively common and extraordinarily diverse group of illnesses; nevertheless, they are at least distantly related by similarities of immunodysregulation. These pathophysiologic relationships are reflected in affected children in similarities of historical, physical, and laboratory data as well as therapeutic intervention.

6/7/3 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE


05619503 EMBASE No: 1994014905
The current and future therapy strategies of rheumatoid **arthritis**

(RA)
GEGENWARTIGE UND ZUKUNFTIGE THERAPIESTRATEGIEN DER RHEUMATOIDEN **ARTHRITIS** (RA)
Schacht E.
Hauptabteilung Med. Wissenschaften, E. Tosse und Co. GmbH, Friedrich-Ebert-Damm 101,22047 Hamburg Germany
Zeitschrift fur Rheumatologie ( Z. RHEUMATOL. ) (Germany) 1993, 52/6 (365-382)
CODEN: ZRHMB ISSN: 0340-1855
DOCUMENT TYPE: Journal; Review
LANGUAGE: GERMAN SUMMARY LANGUAGE: GERMAN; ENGLISH

The triad of inflammation, immunoproliferation and synovial hyperplasiais recognized in the pathogenesis of rheumatoid **arthritis**, however, the sequence of events remains as highly controversial as ever. The 'RA pyramid' was established on the assumption that inflammation is at the top with the destructive processes as sequelae. The moderate successes achieved by conservative therapy with regard to long-term outcome cast doubt on this hypothesis. Inhibitors of prostaglandin synthesis have not been and are not disease modifying. Do substances which influence the endothelial adhesion molecules or leucocyte adhesion receptors (leumedines) promise to be more successful? Do the empirically developed disease modifying antirheumatic drugs (Gold parenteral, MTX) have to be administered earlier? Unfortunately, there is a need for a differential diagnosis which is prognostically valid with regard to the dynamics and aggressiveness of rheumatoid **arthritis**. Moreover, a pharmacological basis for optimally founded combination strategies is also lacking. Presently, the emphasis of research is directed at the regulation of dysfunctional immune systems. Immunosuppressives (cyclosporin A), cytokine antagonists, receptor antagonists and soluble cytokine receptors (IL-1, IL-6, **TNF**-alpha), **antibodies** against lymphocyte subgroups (CDinf 4, CDinf 7) or against cytokines and their receptors are part of the arsenal for the medium term. Too little is still known about the role of protective cytokines (TGF-beta, IL-4, gamma-INF). Currently, however, it is prognosticated that these targeted therapies will only succeed in RA subgroups or only in intelligent combinations. More attractive alternatives are strategic therapy modalities which intervene very early in the pathological process, such as the modulation of antigen presentation (MHC blocking peptides, T-cell receptor antagonists, T-cell vaccination) or the induction of tolerance against autoantigens through the oral administration of antigens (collagen II, HSP's, OM-8980). If the center of the pathological process, however, is found in the synovial proliferation of tumor-like cell clusters, then there are only a few years at the beginning of the disease when there is a real chance to impede destruction. In this case, aggressive induction therapy can be the only key to success. In the future, specifically active cytostatics (inhibitors of angiogenesis) will have to be developed and clinical trials conducted on adjuvant therapies with substances which strengthen bone and cartilage, making them more resistant to aggressive cell clusters (bisphosphonates, calcitonins, metalloproteinase- or collagenase-inhibitors).

6/7/4 (Item 3 from file: 73)


05607492 EMBASE No: 1994010190
Eosinophilia-myalgia syndrome, toxic-oil syndrome, and diffuse fasciitis with eosinophilia
Silver R.M.
Division of Rheumatology/Immunology, Department of Medicine, Medical University of South Carolina, 171 Ashley Avenue,Charleston, SC 29425 United States
Current Opinion in Rheumatology ( CURR. OPIN. RHEUMATOL. ) (United States

) 1993, 5/6 (802-808)
CODEN: CORHE ISSN: 1040-8711
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

6/7/5 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE


05516131 EMBASE No: 1993284230
Future aspects of new therapeutic possibilities of rheumatic diseases
NEUE THERAPEUTISCHE MOGLICHKEITEN. ZUKUNFTSASPEKTE
Rubbert A.; Burmester G.-R.
Inst. fur Klin. Immunol./Rheumatol., Medizinische Klinik III, Universitat Erlangen-Nurnberg, Krankenhausstrasse 12,D-91054 Erlangen Germany
Internist ( INTERNIST ) (Germany) 1993, 34/9 (841-851)
CODEN: INTEA ISSN: 0020-9554
DOCUMENT TYPE: Journal; Review
LANGUAGE: GERMAN SUMMARY LANGUAGE: GERMAN

6/7/6 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE


05266008 EMBASE No: 1993034093
Wegener's granulomatosis
Hoffman G.S.
Rheumatic/Immunologic Diseases Dept., Cleveland Clinic Foundation, 9500 Euclid Avenue,Cleveland, OH 44195 United States
Current Opinion in Rheumatology ( CURR. OPIN. RHEUMATOL. ) (United States ) 1993, 5/1 (11-17)
CODEN: CORHE ISSN: 1040-8711
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

In recent years, interest in Wegener's granulomatosis has been stimulated by an increasing appreciation of the chronic relapsing nature of this disease and its association with antibodies to proteinase 3. Although conventional therapy with cyclophosphamide and glucocorticoids has produced remission in most patients, remission may not occur immediately and, in at least 50% of patients, may be followed by relapse. As a result, most patients experience some form of permanent morbidity from disease or treatment, or both. These observations have led to renewed efforts to identify more effective and less toxic therapies. Preliminary studies have evaluated other cytotoxic agents, such as **methotrexate**, and biologic products, such as high-dose immunoglobulin and monoclonal antibodies. It is hoped that a better understanding of the possible pathogenic role of anti-proteinase 3 antibodies may contribute to improved therapy. Unfortunately, research is handicapped by lack of an animal model, without which it will be difficult to prove convincingly that anti-proteinase 3 antibodies are important in expressing disease.

6/7/7 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE


05215370 EMBASE No: 1992355604
Use of monoclonal antibodies in vivo as a therapeutic strategy for alloimmune or **autoimmune** reactivity: The Besancon experience
Herve P.; Racadot E.; Wendling D.; Rumbach L.; Tiberghien P.; Cahn J.Y.; Flesch M.; Wijdenes J.

Centre Reg. de Transfusion Sanguine, 1 Boulevard Fleming,25020 Besancon France
Immunological Reviews ( IMMUNOL. REV. ) (Denmark) 1992, -/129 (31-55)
CODEN: IMRED ISSN: 0105-2896
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH

6/7/8 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)


07817709 93273249 PMID: 8388844
Rheumatoid **arthritis**: new science, new treatment.
Miller-Blair D J; Robbins D L
Kaiser-Permanente Medical Center, South Sacramento, CA.
Geriatrics (UNITED STATES) Jun **1993**, 48 (6) p28-31, 35-8, ISSN 0016-867X Journal Code: 2985102R
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Rheumatoid **arthritis** (RA) is a chronic systemic inflammatory disease that occurs two to four times as often in women as in men and increases in incidence with advancing age. It affects synovial-lined joints and can also affect the pulmonary, cardiac, nervous, integumentary, and reticuloendothelial systems. RA is manifested clinically by malaise and fatigue, followed by a symmetric pattern of joint inflammation characterized by pain and stiffness. RA most likely occurs in the setting of a genetically predisposed individual, triggered by infectious agents or endogenous antigens. Many of the newer treatments being studied involve blocking cytokine-mediated interactions between cells of the synovium. (18 Refs.)
Record Date Created: 19930629
Record Date Completed: 19930629

6/7/9 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)


07764235 93219728 PMID: 8465132
[If I had chronic polyarthritis--current ideas on basic therapy]
Wenn ich eine chronische Polyarthritis hatte--Neue Ideen zur Basistherapie.
Hasler F
FMH Innere Medizin, speziell Rheumaerkrankungen, Chur.
Schweizerische Rundschau fur Medizin Praxis = Revue suisse de medecine Praxis (SWITZERLAND) Mar 23 **1993**, 82 (12) p349-52, ISSN 1013-2058 Journal Code: 8403202
Document type: Journal Article ; English Abstract
Languages: GERMAN
Main Citation Owner: NLM
Record type: Completed
Rheumatoid **arthritis** (RA) is a chronic inflammatory disorder of largely unknown etiology and complex multifactorial pathogenesis. To date, the medical management has been less than optimal and has consisted primarily of drugs that modulate the acute inflammatory process. Over the years a treatment program referred to as the classical therapeutic pyramid has evolved. A new concept and a controversial one in therapy of RA is that already at the time of definitive diagnosis, a more concerted effort towards vigorous treatment using second-line drugs such as **methotrexate** , should be made. It is very likely that over the next 5 years interventions such as monoclonal **antibodies** directed against

predetermined T-cell subpopulations and anti-cytokines such as **TNF** -alpha binding proteins will evolve as new concepts in therapy of RA.
Record Date Created: 19930506
Record Date Completed: 19930506

6/7/10 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)


06917860 91158187 PMID: 2001072
Increased TNF-alpha secretion by alveolar macrophages from patients with rheumatoid **arthritis**.
Gosset P; Perez T; Lassalle P; Duquesnoy B; Farre J M; Tonnel A B; Capron A
Centre d'Immunologie et de Biologie Parasitaire, Unite mixte INSERM, CNRS, Lille, France.
American review of respiratory disease (UNITED STATES) Mar **1991**, 143 (3) p593-7, ISSN 0003-0805 Journal Code: 0370523
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Tumor necrosis factor alpha (TNF) and interleukin-1 (IL-1) production by alveolar macrophages (AM) was evaluated in 17 rheumatoid **arthritis** (RA) patients without interstitial lung disease (ILD, Group 1) and 14 RA patients with clinical ILD (Group 2) in comparison with 10 control subjects. AM after recovery by bronchoalveolar lavage were selected by adherence, and then supernatants were collected after 3 or 24 h of culture. Results showed no modification of IL-1 synthesis in either group of RA patients. Spontaneous TNF production was significantly increased in Group 2 (2.5 +/- 0.5 ng/ml) as well as in Group 1 (2.4 +/- 0.4 ng/ml) compared with control subjects (0.43 +/- 0.1 ng/ml, p less than 0.001). In addition, AM from patients untreated or treated exclusively by nonsteroidal antiinflammatory drugs produced similar levels of TNF, whereas those receiving corticosteroids, second-line drugs (such as sulfasalazine, aurothiomalate, and **methotrexate**), or the combination of both therapy regimens released significantly less TNF. Interestingly, TNF was not different in both groups, but Group 2 had a markedly increased ratio of local immune complex to albumin in bronchoalveolar lavage fluid (0.47 +/- 0.12 versus 0.07 +/- 0.02 in Group 1; p less than 0.002). TNF thus appears an additional component of RA subclinical alveolitis in RA, but its prognostic value and its precise role in lung damage remain to be determined. Development of ILD requires certainly complex interactions of synergistic factors, possibly including local immune complexes detected in BAL fluids.
Record Date Created: 19910410
Record Date Completed: 19910410
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| S2 | 1727 | S1 AND (AUTOIMMUN? OR ARTHRITIS) |
| S3 | 1077 | (TNF? OR TUMOR(W)NECROSIS OR TUMOUR(W)NECROSIS)(20N)(ANTIBOD?) AND METHOTREXATE |
| S4 | 754 | S3 AND (ARTHRITIS OR AUTOIMMUN?) |
| S5 | 12 | S4 AND PY<1995 |
| S6 | 10 | RD S5 (unique items) |

? e au=feldmann marc ?

| Ref | Items | Index-term |
|---|---|---|
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| E2 | 160 | AU=FELDMANN MARC |

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E3          0 *AU=FELDMANN MARC ?
E4          1  AU=FELDMANN MARCIA L
E5          1  AU=FELDMANN MARIANNE
E6          4  AU=FELDMANN MARK
E7          2  AU=FELDMANN MICHELLE M
E8          2  AU=FELDMANN N
E9          3  AU=FELDMANN N.
E10         4  AU=FELDMANN NICOLE
E11        18  AU=FELDMANN P
E12         1  AU=FELDMANN P D

           Enter P or PAGE for more
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              160  AU=FELDMANN MARC
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           166065  TNF?
      S8       97  S7 AND TNF?
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           121697  METHOTREXATE
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     S11        2  RD S10 (unique items)
? t s11/7/all

 11/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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0012861593   BIOSIS NO.: 200100033432
Infliximab and methotrexate in the treatment of rheumatoid arthritis
AUTHOR: Lipsky Peter E (Reprint); Van Der Heijde Desiree M F M; St Clair E
  William; Furst Daniel E; Breedveld Ferdinand C; Kalden Joachim R; Smolen
  Josef S; Weisman Michael; Emery Paul; Feldmann Marc; Harriman
  Gregory R; Maini Ravinder N
AUTHOR ADDRESS: National Institute of Arthritis and Musculoskeletal and
  Skin Diseases, National Institutes of Health, 9000 Rockville Pike, Bldg.
  10, Rm. 9N228, Bethesda, MD, 20892-1820, USA**USA
JOURNAL: New England Journal of Medicine  343 (22): p1594-1602 November 30,
2000 2000
MEDIUM: print
ISSN: 0028-4793
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background Neutralization of tumor necrosis factor alpha (
  TNF-alpha) for three to six months reduces the symptoms and signs
  of rheumatoid arthritis. However, the capacity of this approach to effect
  a more sustained benefit and its effect on joint damage are not known.
  Methods We treated 428 patients who had active rheumatoid arthritis
  despite methotrexate therapy with placebo or infliximab, a chimeric
  monoclonal antibody against TNF-alpha, in intravenous doses of 3 or
  10 mg per kilogram of body weight every 4 or 8 weeks in combination with
  oral methotrexate for 54 weeks. We assessed clinical responses with
  use of the criteria of the American College of Rheumatology, the quality
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of life with a health-status questionnaire, and the effect on joint damage radiographically. Results The combination of infliximab and **methotrexate** was well tolerated and resulted in a sustained reduction in the symptoms and signs of rheumatoid arthritis that was significantly greater than the reduction associated with **methotrexate** therapy alone (clinical response, 51.8 percent vs. 17.0 percent; P<0.001). The quality of life was also significantly better with infliximab plus **methotrexate** than with **methotrexate** alone. Radiographic evidence of joint damage increased in the group given **methotrexate**, but not in the groups given infliximab and **methotrexate** (mean change in radiographic score, 7.0 vs. 0.6; P<0.001). Radiographic evidence of progression of joint damage was absent in infliximab-treated patients whether or not they had a clinical response. Conclusions In patients with persistently active rheumatoid arthritis despite **methotrexate** therapy, repeated doses of infliximab in combination with **methotrexate** provided clinical benefit and halted the progression of joint damage.

11/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


0012391326 BIOSIS NO.: 200000109639
Infliximab (chimeric, anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant **methotrexate**: A randomised phase III trial
AUTHOR: Maini Ravinder (Reprint); St Clair E William; Breedveld Ferdinand; Furst Daniel; Kalden Joachim; Weisman Michael; Smolen Josef; Emery Paul; Harriman Gregory; **Feldmann Marc**; Lipsky Peter
AUTHOR ADDRESS: The Kennedy Institute of Rheumatology and The Imperial College School of Medicine at Charing Cross Hospital, London, W6 8LH, UK **UK
JOURNAL: Lancet (North American Edition) 354 (9194): p1932-1939 Dec. 4, 1999 1999
MEDIUM: print
ISSN: 0099-5355
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background Not all patients with rheumatoid arthritis can tolerate or respond to **methotrexate**, a standard treatment for this disease. There is evidence that antitumor necrosis factor alpha ( **TNFalpha**) is efficacious in relief of signs and symptoms. We therefore investigated whether infliximab, a chimeric human-mouse anti-**TNFalpha** monoclonal antibody would provide additional clinical benefit to patients who had active rheumatoid arthritis despite receiving **methotrexate**. Methods In an international double-blind placebo-controlled phase III clinical trial, 428 patients who had active rheumatoid arthritis, who had received continous **methotrexate** for at least 3 months and at a stable dose for at least 4 weeks, were randomised to placebo (n=88) or one of four regimens of infliximab at weeks 0, 2, and 6. Additional infusions of the same dose were given every 4 or 8 weeks thereafter on a background of a stable dose of **methotrexate** (median 15 mg/week for gtoreq6 months, range 10-35 mg/wk). Patients were assessed every 4 weeks for 30 weeks. Findings At 30 weeks, the American College of Rheumatology (20) response criteria, representing a 20% improvement from baseline, were achieved in 53, 50, 58, and 52% of patients receiving 3 mg/kg every 4 or 8 weeks or 10 mg/kg every 4 or 8 weeks, respectively, compared with 20% of patients receiving placebo plus **methotrexate** (p<0.001 for each of the four infliximab regimens vs placebo). A 50% improvement was achieved in 29, 27, 26, and 31% of infliximab plus **methotrexate** in the same treatment groups,

compared with 5% of patients on placebo plus **methotrexate** (p<0.001). Infliximab was well-tolerated; withdrawals for adverse events as well as the occurrence of serious adverse events or serious infections did not exceed those in the placebo group. Interpretation During 30 weeks, treatment with infliximab plus **methotrexate** was more efficacious than **methotrexate** alone in patients with active rheumatoid arthritis not previously responding to **methotrexate**.

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? ds

Set     Items   Description
S1       2871   (TNF? OR TUMOR(W)NECROSIS OR TUMOUR(W)NECROSIS) AND METHOT-
            REXATE
S2       1727   S1 AND (AUTOIMMUN? OR ARTHRITIS)
S3       1077   (TNF? OR TUMOR(W)NECROSIS OR TUMOUR(W)NECROSIS)(20N)(ANTIB-
            OD?) AND METHOTREXATE
S4        754   S3 AND (ARTHRITIS OR AUTOIMMUN?)
S5         12   S4 AND PY<1995
S6         10   RD S5 (unique items)
S7        161   E1-E2
S8         97   S7 AND TNF?
S9         91   RD S8 (unique items)
S10         2   S9 AND METHOTREXATE
S11         2   RD S10 (unique items)
? s s2 and py<1995
Processing
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        36149661  PY<1995
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? rd s12
...examined 50 records  (50)
...completed examining records
     S13      54  RD S12 (unique items)
? t s13/7/all

 13/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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0009614371   BIOSIS NO.: 199598082204
Circulating concentrations and production of cytokines and soluble
  receptors in rheumatoid arthritis patients: Effects of a single
  dose methotrexate
AUTHOR: Barrera P (Reprint); Boerbooms A M T; Demacker P N M; Van De Putte
  L B A; Gallati H; Van Der Meer J W M
AUTHOR ADDRESS: Dep. Rheumatol., Univ. Hosp., Nijmegen, Netherlands**
  Netherlands
JOURNAL: British Journal of Rheumatology  33 (11): p1017-1024 1994
1994
ISSN: 0263-7103
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Methotrexate (MTX) is an effective treatment for RA and its
  effects may be partly due to cytokine modulation. Herein, we assessed the
  effects of a single MTX dose on the production and circulating
  concentrations of several cytokines and soluble receptors in 42 RA
  patients on three consecutive days. Three patient groups were studied:
  (a) 16 patients taking the first MTX dose, (b) 11 patients on chronic MTX
  treatment and (c) a control group of 15 patients not treated with MTX.
  Cytokine production was studied in peripheral blood mononuclear cells
  (PBMNC) and in a whole-blood culture system (WBCS). Group (a) had a more
  active disease according to laboratory parameters as well as higher
  circulating IL-6 levels (P = 0.002). The secretion of IL-1-beta by
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stimulated PBMNC (P = 0.008) was higher in this group and decreased significantly (P = 0.03) after a single MTX dose. No significant change in any parameter was observed after MTX in group (b). In the total patient group, circulating concentrations of IL-1-beta and **TNF**-alpha were low but blood cells showed a high capacity of production for these cytokines. In contrast for sTNFRs, high circulating levels but a limited in vitro production were observed. In conclusion, a single MTX dose may result in decreased production of IL-1-beta by PBMNC in patients with active RA. Furthermore, we observed an imbalance in the production of **TNF**-alpha and sTNFRs by peripheral blood cells of RA patients and propose that the WBCS is convenient for studying cytokine production in RA.

13/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


0009124275 BIOSIS NO.: 199497145560
Serum levels of interleukin-6 and **tumour-necrosis**-factor-alpha are not correlated to disease activity in patients with rheumatoid **arthritis** after treatment with low-dose **methotrexate**
AUTHOR: Wascher Thomas C (Reprint); Hermann J; Brezinschek R; Brezinschek H P; Wilders-Trusching M; Rainer F; Krejs G J
AUTHOR ADDRESS: Dep. Med., Auenbruggerpl. 15, A-8036 Graz, Austria**Austria
JOURNAL: European Journal of Clinical Investigation 24 (1): p73-75 1994 **1994**
ISSN: 0014-2972
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cytokines are major mediators of inflammatory responses in rheumatoid **arthritis**. Some of them have been shown to correlate with the disease activity and thus are proposed to be used for monitoring patients. Therefore the effects of a low-dose therapy with **methotrexate** on serum concentrations of interleukin-6 (IL-6) and **tumour-necrosis**-factor-alpha (**TNF**-alpha) were examined in eight patients with seropositive rheumatoid **arthritis**. Serum levels of IL-6 and **TNF**-alpha were significantly elevated in patients compared to healthy controls. Before the onset of MTX treatment IL-6 concentrations were correlated to the c-reactive protein (P lt 0.05) but the correlation was abolished after treatment. For **TNF**-alpha no correlations neither before nor after treatment were observed. Both cytokines remained substantially elevated after MTX treatment despite a clear reduction in disease activity. Thus we suggest that one of the effects of MTX might be the inhibition of some of the actions of IL-6 and **TNF**-alpha.

13/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


0009020892 BIOSIS NO.: 199497042177
Elevated levels of **TNF** in the joints of adjuvant arthritic rats
AUTHOR: Smith-Oliver Tracey; Noel L Staton; Stimpson Steven S; Yarnall David P; Connolly Kevin M (Reprint)
AUTHOR ADDRESS: Dep. Immunology, Glaxo Res. Inst., Five Moore Drive, Research Triangle Park, NC 27709, USA**USA
JOURNAL: Cytokine 5 (4): p298-304 1993 **1993**
ISSN: 1043-4666
DOCUMENT TYPE: Article
RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The primary purpose of this study was to determine whether local levels of **tumor necrosis** factor (**TNF**) were elevated in chronically inflamed joints in rats with adjuvant-induced **arthritis** (AA). We also wished to develop methodology for the quantitative measurement of joint **TNF**, and to examine the effects of known anti-inflammatory agents on joint **TNF** levels. **TNF** levels were measured in joints from AA rats taken during the systemic phase (day 20) of arthritic disease. Using the L929 bioassay, joint extracts from AA rats had significantly greater **TNF** levels (1054 +- 147 pg/g tissue) than joint extracts from normal rats (110 +- 42 pg/g tissue). Administration of ibuprofen failed to significantly inhibit **TNF** levels in the joint at a time point when paw swelling was significantly reduced. The immunomodulating agents, **methotrexate**, cyclosporin A (CSA) and HWA486 profoundly inhibited both joint **TNF** levels and paw swelling. The specificity of this assay for **TNF** was supported by studies with a polyclonal rabbit anti-mouse **TNF** antibody which neutralized 78-87% of the **TNF** activity in the joint extracts. Our studies demonstrate a quantitative increase in local **TNF** expression in adjuvant **arthritis** and support a role for **TNF** in chronic inflammation.

13/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


0009000851 BIOSIS NO.: 199497022136
**Methotrexate** (MTX) therapy is associated with a reduction of **TNF**-alpha (**TNF**-a) an soluble **TNF** receptor (**TNF**-R) levels in serum of patients with psoriatic **arthritis** (PA) but not with rheumatoid **arthritis** (RA)
AUTHOR: Leeb B F; Studnicka-Benke A; Steiner G; Smolen J S
AUTHOR ADDRESS: Second Dep. Med., Lainz Hospital, Vienna, Austria**Austria
JOURNAL: Arthritis and Rheumatism 36 (9 SUPPL.): pA80 1993 **1993**
CONFERENCE/MEETING: 57th Annual Scientific Meeting of the American College of Rheumatology San Antonio, Texas, USA November 7-11, 1993; 19931107
ISSN: 0004-3591
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

13/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


0008935483 BIOSIS NO.: 199396099899
Circulating soluble **tumor necrosis** factor receptors, interleukin-2 receptors, **tumor necrosis** factor alpha, and interleukin-6 levels in rheumatoid **arthritis**: Longitudinal evaluation during **methotrexate** and azathioprine therapy
AUTHOR: Barrera Pilar (Reprint); Boerbooms Agnes M T; Janssen Elly M; Sauerwein Robert W; Gallati H; Mulder Jan; De Boo Theo; Demacker Pierre N M; Van Der Putte Levinus B A; Van Der Meer Jos W M
AUTHOR ADDRESS: Dep. Rheumatol. Internal Med., Univ. Hosp. Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, Netherlands**Netherlands
JOURNAL: Arthritis and Rheumatism 36 (8): p1070-1079 **1993**
ISSN: 0004-3591
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Objective. To assess whether circulating concentrations of soluble **tumor necrosis** factor receptors (sTNFR; p55 and p75), soluble interleukin-2 receptors (sIL-2R), **tumor necrosis** factor a (**TNF**-alpha), and interleukin-6 (IL-6) reflect clinical response and whether changes are dependent on the drug used in rheumatoid **arthritis** (RA) patients taking **methotrexate** (MTX) or azathioprine (AZA). were assessed in 20 control subjects and serially for up to 48 weeks in 61 RA patients, by bioassay (IL-6) and immunoassays (sTNFR, sIL-2R, **TNF**-alpha, and IL-6). Results. Concentrations of p55 and p75, sIL-2R, and **TNF**-alpha (but not IL-6) were significantly higher in RA patients than in controls. Significant decreases in sIL-2R and p55 concentrations were associated with clinical improvement and were observed in patients treated with, MTX, but not AZA. Both treatments induced decreases in IL-6 concentrations, but circulating AZA (or its metabolites) appears to interfere with the measurement of IL-6 bioactivity. **TNF**-alpha and p75 levels did not show significant changes. Conclusion. Measurement of circulating sIL-2R, p55, and IL-6 may be useful in the evaluation of RA disease activity and response to therapy. Interference by circulating levels of drugs must be ruled out when bioassays are used to evaluate cytokine levels.

13/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


0008453791 BIOSIS NO.: 199344016686
Effect of **methotrexate**-phospholipid conjugates upon mediator release by macrophages
AUTHOR: Williams A S (Reprint); Amos N; Topley M; Williams B D
AUTHOR ADDRESS: Dep. Rheumatol., Univ. Hosp., Cardiff CF4 4XN, UK**UK
JOURNAL: Arthritis and Rheumatism 35 (9 SUPPL.): pS309 **1992**
CONFERENCE/MEETING: 56th Annual Scientific Meeting of the American College of Rheumatology, Atlanta, Georgia, USA, October 11-15, 1992. ARTHRITIS RHEUM
ISSN: 0004-3591
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: English

13/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


0008453781 BIOSIS NO.: 199344016676
**Methotrexate** and azathioprine therapy for rheumatoid **arthritis**: Effects on circulating cytokines
AUTHOR: Barrera P; Janssen E M; Sauerwein R W; Boerbooms A M T; Van De Putte L B A; Van Der Meer J W M
AUTHOR ADDRESS: Dep. Rheumatol. Internal Med., Univ. Hosp. Nijmegen, Netherlands Antilles**Netherlands Antilles
JOURNAL: Arthritis and Rheumatism 35 (9 SUPPL.): pS307 **1992**
CONFERENCE/MEETING: 56th Annual Scientific Meeting of the American College of Rheumatology, Atlanta, Georgia, USA, October 11-15, 1992. ARTHRITIS RHEUM
ISSN: 0004-3591
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: English

13/7/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0008341467 BIOSIS NO.: 199294043308
THE EFFECT OF SLOW-ACTING ANTI-RHEUMATIC DRUGS SAARDS AND COMBINATIONS OF SAARDS ON MONOKINE PRODUCTION IN-VITRO
AUTHOR: DANIS V A (Reprint); FRANIC G M; BROOKS P M
AUTHOR ADDRESS: KOLLING INST, ROYAL NORTH SHORE HOSP, ST LEONARDS, NSW 2065, AUST**AUSTRALIA
JOURNAL: Drugs under Experimental and Clinical Research 17 (12): p549-554 **1991**
ISSN: 0378-6501
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The mode of action of slow-acting anti-rheumatic drugs (SAARDs) is complex but may often include effects of cytokine (interleukin-1, IL-1, and **tumour necrosis** factor, **TNF**) production by monocytes/macrophages. Different SAARDs. May have variable effects on cytokine production in vitro depending on the concentration of drug, the presence of other SAARDs and individual variation. The gold compounds gold sodium thiomalate (GST) and auranofin (AF) had a bimodal effect on cytokine production. High concentrations of GST (> 1 .mu.g/ml) weakly inhibited IL-1-.beta. secretion (without affecting IL-1-.alpha. or **TNF** secretion and without affecting cell-associated IL-1-.alpha. and IL-1-.beta. accumulation), and although AF (> 100 ng/ml) inhibited cytokine production it did so at concentrations near to the toxic range for the drug (> 200 ng/ml). GST and AF when used in combination inhibited cytokine production in a synergistic manner even at concentrations that would potentiate cytokine production if used individually. Hydroxychloroquine (HCQ) and sulfasalazine (SAP) were two other inhibitory SAARDs which acted synergistically in combination. Combination of HCQ and SAP with gold drugs gave variable results. D-penicillamine (D-pen) and **methotrexate** (MTX) were two SAARDs that generally did not affect cytokine production individually or in combination with other SAARDs. These results suggest that combination SAARD therapy may more effectively target excessive cytokine production, which is a hallmark of rheumatoid **arthritis**.

13/7/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


0007907302 BIOSIS NO.: 199242010193
EFFECTS OF A WEEKLY DOSES OF **METHOTREXATE** ON IL-1 **TNF** AND IL-6 IN PATIENTS WITH RHEUMATOID **ARTHRITIS**
AUTHOR: BARRERA P (Reprint); JANSSEN E M; BOERBOOMS A M T; VAN DE PUTTE L B A; SAUERWEIN R W; VAN DER MEER J W M
AUTHOR ADDRESS: UNIV HOSPITAL NIJMEGEN, POSTBOX 9101, NETHERLANDS** NETHERLANDS
JOURNAL: Cytokine 3 (5): p504 **1991**
CONFERENCE/MEETING: THIRD INTERNATIONAL WORKSHOP ON CYTOKINES, STRESA, ITALY, NOVEMBER 10-14, 1991. CYTOKINE.
ISSN: 1043-4666
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH

13/7/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0007747592  BIOSIS NO.: 199191130483
INCREASED **TNF**-ALPHA SECRETION BY ALVEOLAR MACROPHAGES FROM PATIENTS WITH RHEUMATOID **ARTHRITIS**
AUTHOR: GOSSET P (Reprint); PEREZ T; LASSALLE P; DUQUESNOY B; FARRE J M; TONNEL A B; CAPRON A
AUTHOR ADDRESS: CENTRE IMMUNOLOGIE BIOLOGIE PARASITAIRE, UNITE MIXTE INSERM 167, CNRS 624, BP 245, INSTITUT PASTEUR, 59019 LILLE CEDEX, FR**FRANCE
JOURNAL: American Review of Respiratory Disease 143 (3): p593-597 **1991**
ISSN: 0003-0805
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: **Tumor necrosis** factor .alpha. (**TNF**) and interleukin-1 (IL-1) production by alveolar macrophages (AM) was evaluated in 17 rheumatoid **arthritis** (RA) patients without interstitial disease (ILD, Group 1) and 14 RA patients with clinical ILD (Group 2) in comparison with 10 control subjects. AM after recovery by bronchoalveolar lavage were selected by adherence, and then supernatants were collected after 3 or 24 h of culture. Results showed no modification of IL-1 synthesis in either group of RA patients. Spontaneous **TNF** production was significantly increased in Group 2 (2.5 .+-. 0.5 ng/ml) as well as in Group 1 (2.4 .+-. 0.4 ng/ml) compared with control subjects (0.43 .+-. 0.1 ng/ml, $p < 0.001$). In addition, AM from patients untreated or treated exclusively by nonsteroidal antiinflammatory drugs produced similar levels of **TNF**, whereas those receiving corticosteroids, second-line drugs (such as sulfasalzine, aurothiomalate, and **methotrexate**), or the combination of both therapy regimens released significantly less **TNF**. Interestingly, **TNF** was not different in both groups, but Group 2 had a markedly increased ratio of local immune complex to albumin in bronchoalveolar lavage fluid (0.47 .+-. 0.12 versus 0.07 .+-. 0.02 in Group 1; $p < 0.002$). **TNF** thus appears an additional component of RA subclinical alveolitis in RA, but its prognostic value and its precise role in lung damage remain to be determined. Development of ILD requires certainly complex interactions of synergistic factors, possibly including local immune complexes detected in BAL fluids.

13/7/11  (Item 11 from file: 5)


0007390929  BIOSIS NO.: 199140033820
**METHOTREXATE** MECHANISM OF ACTION IN RHEUMATOID **ARTHRITIS**
AUTHOR: SEGAL R (Reprint); YARON M; TARTAKOVSKY B
AUTHOR ADDRESS: DEP RHEUMATOLOGY, ICHILOV HOSP, TEL-AVIV 64239, ISRAEL** ISRAEL
JOURNAL: Seminars in Arthritis and Rheumatism 20 (3): p190-200 **1990**
ISSN: 0049-0172
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: ENGLISH

13/7/12  (Item 12 from file: 5)


0006488745  BIOSIS NO.: 198937066494
EFFECTS OF **TUMOR NECROSIS** FACTOR AND COMBINATION CYCLOSPORIN A-**METHOTREXATE** THERAPY ON COLLAGEN **ARTHRITIS**
AUTHOR: BRAHN E (Reprint); BANQUERIGO M L C; LIU D Y

AUTHOR ADDRESS: UCLA SCH MED, LOS ANGELES, CALIF 90024, USA**USA
JOURNAL: Arthritis and Rheumatism 32 (4 SUPPL): pS133 **1989**
CONFERENCE/MEETING: 53RD ANNUAL SCIENTIFIC MEETING OF THE AMERICAN COLLEGE OF RHEUMATOLOGY, CINCINNATI, OHIO, USA, JUNE 12-17, 1989. ARTHRITIS RHEUM.
ISSN: 0004-3591
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH

13/7/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


0006439836 BIOSIS NO.: 198937017585
ELEVATION OF AN IMPORTANT LYMPHOKINE IL-2 AND MONOKINE **TNF** IN THE SERUM OF PATIENTS WITH PRIMARY BILIARY CIRRHOSIS **AUTOIMMUNITY**
AUTHOR: DEMPSEY R A (Reprint); MILLER L C; CASTRACANE J M; DINARELLO C A
AUTHOR ADDRESS: ENDOGEN INC, BOSTON, MASS, USA**USA
JOURNAL: FASEB Journal 3 (4): pA1121 **1989**
CONFERENCE/MEETING: 73RD ANNUAL MEETING OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, NEW ORLEANS, LOUISIANA, USA, MARCH 19-23, 1989. FASEB (FED AM SOC EXP BIOL) J.
ISSN: 0892-6638
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH

13/7/14 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE


05942930 EMBASE No: 1994355211
Preliminary report of radical multiple synovectomy in rheumatoid **arthritis**
Yoshino S.; Koiwa M.; Kowada M.; Nagashima S.; Nishioka K.
Department of Joint Disease, Nippon Medical School,Chiyoda-ku, Tokyo Japan
Ryumachi ( RYUMACHI ) (Japan) 1994, 34/5 (908-913)
CODEN: RYMCA ISSN: 0300-9157
DOCUMENT TYPE: Journal; Article
LANGUAGE: JAPANESE SUMMARY LANGUAGE: ENGLISH

We performed radical multiple synovectory (RaMS) on rheumatoid **arthritis** (RA) patients who had multiple swollen joints in the mid or late course of RA. The objectives of this operation are to reduce the quantity of RA synovium as much as possible and to increase the efficacy of anti-rheumatic medication in order to achieve remission. Nineteen RA patients who underwent RaMS were followed up for at least 15 months. In this series, anti-rheumatic medications were not changed after the operation, so that the effectiveness of the RaMS could be evaluated. The patients ranged in age from 44 to 73 years (mean: 55.8 years). The male to female ratio was 2:17. Duration after onset of RA ranged from 2 to 29 years (mean: 15.1 years). The swollen joint score according to Lansbury's evaluation of the RA activity index ranged from 7 to 24% (mean: 14.4%). The synovectomized joint score ranged from 7 to 22% (mean: 13.3%). The weight of the excised RA synovium ranged from 19.0 to 109.9 g (mean: 54.0 g). The number of operations was one in three patients, two in 15 patients and three in one patient. The postoperative results indicated that the modified Lansbury's index (morning stiffness, grip power, ESR, joint score), the values of ESR, CRP, Hb, **TNF**-alpha and IL-6 in the blood, and the peripheral lymphocyte CDinf 4/CDinf 8 ratio were improved, with a statistically significant difference. At 15 months after the operation, ten

of the 19 patients (52.5%) satisfied the proposed criteria for clinical remission of RA. In addition, six of the 19 patients had recurrence of swelling in a few joints in the operated joints after RaMS. Duration of illness was significantly longer in patients in whom remission was achieved than in those in whom it was not. Examinations conducted upon admission showed significantly higher value of Hb and lower value of serum IL-6 in the former than in the latter. Modified Lansbury's index and values of ESR, joint score and peripheral lymphocyte CDinf 4/CDinf 8 ratio showed significant improvement during the postoperative observation period compared to findings obtained before surgery, both in patients in whom remission was achieved and in those in whom it was not, while values of CRP and IL-6 in the blood significantly decreased only in the former. These results indicate that RaMS is effective in the treatment of RA in the mid and late course. This suggests that the quantity of RA synovium in the whole body influences the efficacy of anti-rheumatic medication.

13/7/15 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE


05925316 EMBASE No: 1994339223
Gold sodium thiomalate down-regulates intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 expression on vascular endothelial cells

Koike R.; Miki I.; Otoshi M.; Totsuka T.; Inoue H.; Kase H.; Saito I.; Miyasaka N.
Division of Immunological Diseases, Medical Research Institute, Tokyo Medical and Dental University, 1-5-45, Yushima,Bunkyo-ku, Tokyo Japan
Molecular Pharmacology ( MOL. PHARMACOL. ) (United States) 1994, 46/4 (599-604)
CODEN: MOPMA ISSN: 0026-895X
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

We examined whether antirheumatic drugs alter cytokine- or lipopolysaccharide-induced expression of adhesion molecules on vascular endothelial cells. Human umbilical cord vein endothelial cells were co-cultured with various antirheumatic drugs in the presence of inflammatory cytokines, and adhesion molecule expression was measured by cell enzyme-linked immunosorbent assay and Northern blot analysis. Among these antirheumatic drugs, gold sodium thiomalate significantly inhibited intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 expression on vascular endothelial cells and suppressed cellular binding between human monocytic cell lines, including U937 and HL-60 cells, and interleukin-1beta-stimulated vascular endothelial cells. It is speculated that down-regulation of adhesion molecules might be one of the novel mechanisms of action of gold sodium thiomalate.

13/7/16 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE


05914583 EMBASE No: 1994323839
Systemic cytokine measurements: Their role in monitoring the response to therapy in patients with rheumatoid **arthritis**

Luqmani R.; Sheeran T.; Robinson M.; Richardson K.; Winkles J.; Emery P.
Department of Rheumatology, University of Birmingham,Edgbaston, Birmingham B15 2TT United Kingdom
Clinical and Experimental Rheumatology ( CLIN. EXP. RHEUMATOL. ) (Italy) 1994, 12/5 (503-508)
CODEN: CERHD ISSN: 0392-856X
DOCUMENT TYPE: Journal; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Objective. To determine the value of serial measurements of circulating cytokines in patients with rheumatoid **arthritis** in response to the introduction of disease modifying anti-rheumatic drugs (DMARDs). Methods. A prospective 12-week study of 98 patients starting second line therapy with serial measurements of IL1 beta, IL2 receptor, IL6, **TNF**, and urinary neopterins as well as ESR, CRP and rheumatoid factor. Results. The markers of the acute phase response fell significantly with treatment as did the rheumatoid factor. IL-6 fell in certain sub-groups (significantly so after sulphasalazine SZP) of treated patients, but no other consistent change in circulating cytokine levels was demonstrated. Urinary neopterins rose with therapy. Conclusions. The measurement of circulating cytokine levels in patients with rheumatoid **arthritis** is of limited benefit; macrophage function (as measured by urinary neopterins) is initially enhanced by DMARDs in patients with rheumatoid **arthritis**.

13/7/17 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE


05911451 EMBASE No: 1994318125
Type VI collagen-specific messenger RNA is expressed constitutively by cultured human synovial fibroblasts and is suppressed by interleukin-1
Bathon J.M.; Hwang J.J.; Shin L.H.; Precht P.A.; Towns M.C.; Horton Jr. W.E.
Johns Hopkins Asthma/Allergy Center, 5501 Hopkins Bayview Circle,Baltimore, MD 21224 United States
Arthritis and Rheumatism ( ARTHRITIS RHEUM. ) (United States) 1994, 37/9 (1350-1356)
CODEN: ARHEA ISSN: 0004-3591
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Objective. Type VI collagen is a prominent constituent of the synovial extracellular matrix. The cellular source of this matrix protein and the identity of local factors in synovium that may regulate its expression have not been delineated, however. We examined the capacity of human fibroblast-like synovial cells to synthesize type VI collagen as well as the effect of interleukin-1 (IL-1) on this expression. Methods. RNA was extracted from cultured human synovial cells derived from patients with rheumatoid **arthritis** (RA) and osteoarthritis (OA). Northern blots were analyzed using sequence- specific probes, and steady-state messenger RNA (mRNA) levels of the 3 alpha(VI) procollagen chains were measured. The effect of IL-1 treatment on these levels was determined. Results. Abundant expression of 3 characteristic mRNA transcripts, corresponding to the alpha1 (4.2-kb), alpha2 (3.5-kb), and alpha3 (8.5- kb) chains of type VI procollagen, was observed in untreated cells derived from RA and OA patients. IL-1 treatment consistently suppressed steady-state mRNA levels for all 3 alpha(VI) procollagen chains in a time- and dose-dependent manner. **Tumor necrosis** factor alpha induced a response similar to that of IL-1, while IL-2 was ineffective in this regard. Indomethacin partially restored alpha(VI) mRNA expression in IL-1-treated cells. Conclusion. These studies provide novel data demonstrating abundant steady-state levels of mRNA transcripts coding for all 3 type VI procollagen polypeptides in human synovial fibroblast-like cells, as well as coordinated down-regulation of these transcripts by IL-1. Local production of IL-1 may thus constitute an important means in vivo of regulating the production of type VI collagen.

13/7/18 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

05911137 EMBASE No: 1994320449
Prostaglandin and **tumor necrosis** factor secretion by peritoneal macrophages isolated from normal and arthritic rats treated with liposomal **methotrexate**
Williams A.S.; Camilleri J.P.; Topley N.; Williams B.D.
Rheumatology Research Laboratory, Univ. of Wales College of Medicine, Heath Park,Cardiff, CF4 4XN United Kingdom
Journal of Pharmacological and Toxicological Methods ( J. PHARMACOL. TOXICOL. METHODS ) (United States) 1994, 32/1 (53-58)
CODEN: JPTME ISSN: 1056-8719
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The effect of a novel liposomal preparation containing a phospholipid conjugate of **methotrexate** (MTX-LIPO) upon macrophage mediator release was investigated in normal and arthritic rats ex vivo. Peritoneal macrophages isolated from MTX-LIPO-treated arthritic rats and stimulated with lipopolysaccharide produced significantly less **tumor necrosis** factor (**TNF**) and prostaglandin (PGEinf 2) than did macrophages isolated from saline-treated controls. In the same experimental system, free **methotrexate** only inhibited prostaglandin release, but it was more potent than MTX-LIPO in this respect. Additional studies are presently underway to investigate the effect of MTX-LIPO and MTX treatment upon the lipopolysaccharide-induced rise in plasma levels of various proinflammatory mediators in vivo. Haematopoietic toxicity was demonstrated in blood isolated from rats treated with free MTX, and this was as characterized by a significant reduction in reticulocyte count compared with MTX-LIPO and saline-treated rats.

13/7/19 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE


05848476 EMBASE No: 1994259688
Circadian rhythm of serum interleukin-6 in rheumatoid **arthritis**
Arvidson N.G.; Gudbjornsson B.; Elfman L.; Ryden A.-C.; Totterman T.H.; Hallgren R.
Section of Rheumatology, Department of Medicine, Uppsala University Hospital,S-751 85 Uppsala Sweden
Annals of the Rheumatic Diseases ( ANN. RHEUM. DIS. ) (United Kingdom) 1994, 53/8 (521-524)
CODEN: ARDIA ISSN: 0003-4967
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Objectives - To test the hypothesis of a diurnal variation in circulating levels of interleukin-6 (IL-6) and/or **tumour necrosis** factor-alpha (**TNF**-alpha) in rheumatoid **arthritis** and other inflammatory connective tissue diseases. Methods - Serum levels of IL-6 and **TNF**-alpha were measured at three hour intervals from 7:30 to 22:30 in 48 patients with different rheumatic diseases as well as ten healthy controls. In four of the patients with rheumatoid **arthritis**, serum IL-6 levels were measured before and after one week of treatment with prednisolone 15-20 mg daily. Results - IL-6 and **TNF**-alpha could not be detected in serum from healthy controls. However, serum IL-6 levels were substantially increased in patients with rheumatoid **arthritis**. Furthermore, patients with rheumatoid **arthritis** showed a statistically significant circadian variation in levels of IL-6. Peak values appeared in the morning and low values in the afternoon and evening. In contrast, levels were low and stable in other connective tissue diseases. Levels of **TNF**-alpha were low in patients with rheumatoid **arthritis** and high in patients with other connective tissue diseases,

but without circadian rhythm. After treatment with prednisolone, levels of serum IL-6 decreased significantly, but the circadian rhythm remained. Conclusions - The circadian rhythm of circulating IL-6 might correspond to the circadian rhythm of symptoms in rheumatoid **arthritis**. The diurnal variation of IL-6, and possibly other cytokines, might explain the conflicting results previously reported on the inter-relationship between circulating IL-6 levels and disease activity in rheumatoid **arthritis**.

13/7/20 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE


05844001 EMBASE No: 1994250587
Augmented expression of inflammatory cytokines and adhesion molecules in accelerated nodulosis during **methotrexate** therapy (5)
Miyasaka N.; Saito I.; Uemura T.; Kashiwazaki S.
Division of Immunological Diseases, Medical Research Institute, Tokyo Medical/Dental University, 1-5-45 Yushima,Bunkyo-ku, Tokyo 113 Japan
Annals of the Rheumatic Diseases ( ANN. RHEUM. DIS. ) (United Kingdom) 1994, 53/7 (480-481)
CODEN: ARDIA ISSN: 0003-4967
DOCUMENT TYPE: Journal; Letter
LANGUAGE: ENGLISH

13/7/21 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE


05841072 EMBASE No: 1994253153
Pediatric rheumatic diseases
Warren R.W.; Perez M.D.; Wilking A.P.; Myones B.L.
Department of Pediatrics, Baylor College of Medicine, One Baylor Plaza,Houston, TX 77030 United States
Pediatric Clinics of North America ( PEDIATR. CLIN. NORTH AM. ) (United States) 1994, 41/4 (783-818)
CODEN: PCNAA ISSN: 0031-3955
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The rheumatic diseases of childhood are a relatively common and extraordinarily diverse group of illnesses; nevertheless, they are at least distantly related by similarities of immunodysregulation. These pathophysiologic relationships are reflected in affected children in similarities of historical, physical, and laboratory data as well as therapeutic intervention.

13/7/22 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE


05826408 EMBASE No: 1994236066
Research in pediatric rheumatology
Glass D.N.; Nepom B.S.; White P.H.; Shulman L.E.
Children's Hospital Medical Center, Cincinnati Univ. College of Medicine,Cincinnati, OH 45229-3039 United States
Journal of Rheumatology ( J. RHEUMATOL. ) (Canada) 1994, 21/7 (1347-1351)
CODEN: JRHUA ISSN: 0315-162X
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH

13/7/23 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE


05734540 EMBASE No: 1994145017
Monoclonal antibodies in the treatment of rheumatoid **arthritis**
Delafuente J.C.; Resman-Targoff B.H.
Department of Pharmacy Practice, University of Florida, PO Box 100486,Gainesville, FL 32610 United States
Annals of Pharmacotherapy ( ANN. PHARMACOTHER. ) (United States) 1994, 28/5 (650-655)
CODEN: APHRE ISSN: 1060-0280
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH

13/7/24 (Item 11 from file: 73)
DIALOG(R)File 73:EMBASE


05708790 EMBASE No: 1994113521
Basic drugs in the treatment of rheumatic diseases and new approaches with immunomodulating agents
BASISTHERAPEUTIKA BEI RHEUMA UND NEUE ANSATZE MIT IMMUNMODULATOREN
Metz G.
Auf dem Rucken 29,89143 Blaubeuren Germany
Pharmazeutische Zeitung ( PHARM. ZTG. ) (Germany) 1994, 139/14 (9-18)
CODEN: PZSED ISSN: 0031-7136
DOCUMENT TYPE: Journal; Short Survey
LANGUAGE: GERMAN SUMMARY LANGUAGE: GERMAN

13/7/25 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE


05704537 EMBASE No: 1994122032
Effect of three lipophilic **methotrexate** derivatives upon mediator release by lipopolysaccharide-stimulated rat peritoneal macrophages
Williams A.S.; Topley N.; Amos N.; Williams B.D.
Rheumatology Research Laboratory, University of Wales College of Med,Heath Park, Cardiff CF4 4XN United Kingdom
Journal of Pharmacy and Pharmacology ( J. PHARM. PHARMACOL. ) (United Kingdom) 1994, 46/4 (291-295)
CODEN: JPPMA ISSN: 0022-3573
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The ability of **methotrexate** and three lipophilic derivatives ( **methotrexate**-gamma-dimyristoylphosphatidylethanolamine (MgammaD), **methotrexate**-alpha-dimyristoylphosphatidylethanolamine (MalphaD) and **methotrexate**-alpha-gamma-di-dimyristoylphosphatidylethanolamine (MalphagammaD) to modulate mediator release by lipopolysaccharide-stimulated rat peritoneal macrophages was investigated. At nontoxic concentrations, approximately 10 nmol/10sup 5 cells, MalphaD and MgammaD produced 11.06 +/- 1.0 and 75.6 +/- 5.2%, respectively, inhibition of **tumour necrosis** factor (**TNF**) release (mean +/- s.e.m., n = 4). At this same dose MalphagammaD resulted in 68.8 +/- 2.1% inhibition of **TNF** but cellular ATP levels were reduced by 80%. The inhibitory activity of all three derivatives was dose-dependent. Non-derivatized **methotrexate** at a concentration of 25 nmol/10sup 5 cells had no inhibitory effect upon **TNF** release (14.7 +/- 0.8%, n = 3). Determination of prostaglandin Einf 2 (PGEinf 2) levels in the same

samples demonstrated that all three conjugates were powerful inhibitors of prostaglandin release. At a quarter of the conjugate concentrations described above the monoamides MalphaD (3.1 nmol/10sup 5 cells) and MgammaD (2.5 nmol/10sup 5 cells) maintained their effects on PGEinf 2 production with 73 +/- 2.3 and 71 +/- 2.0% (n = 4) inhibition, respectively. At this lower concentration, however, the diamide MalphagammaD (3.1 nmol/10sup 5 cells) was less effective in reducing the amount of PGEinf 2 released from the macrophages (29 +/- 18%, n = 4). Maximal PGEinf 2 inhibition by each of the conjugates was attained at approximately 5 nmol/10sup 5 cells. Unconjugated **methotrexate** (range of 2.5-20 nmol/10sup 5 cells) did not inhibit the release of PGEinf 2 from lipopolysaccharide-stimulated macrophages.

13/7/26 (Item 13 from file: 73)
DIALOG(R)File 73:EMBASE


05698588 EMBASE No: 1994110945
Immunosuppression in the treatment of disease
Dickler H.B.; Albright J.F.
National Institutes of Health, Solar Building,Bethesda, MD 20892 United States
Journal of Allergy and Clinical Immunology ( J. ALLERGY CLIN. IMMUNOL. ) (United States) 1994, 93/3 (669-676)
CODEN: JACIB ISSN: 0091-6749
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH

13/7/27 (Item 14 from file: 73)
DIALOG(R)File 73:EMBASE


05657234 EMBASE No: 1994070548
Novel immunosuppressive and antiinflammatory drugs: A 1993 perspective
Allison A.C.
Dawa Corporation,Belmont, CA United States
Annals of the New York Academy of Sciences ( ANN. NEW YORK ACAD. SCI. ) ( United States) 1993, 696/- (XI-XX)
CODEN: ANYAA ISSN: 0077-8923
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Research on immunosuppressive and antiinflammatory drugs is progressing rapidly. Several new drugs are in development, and learning how to combine them optimally, for treatment of different diseases and prolonging graft survival, will be a major task for the next few years. Decreasing the incidence of complications following transplantation will reduce patient anxiety and cost, and the shortage of donor organs is an additional reason for wishing to prolong graft acceptance. Many clinical findings with the new drug combinations should be published by the end of the century. We can begin the next millennium with improved immunosuppressive and antiinflammatory drugs discussed at the Orlando conference.

13/7/28 (Item 15 from file: 73)
DIALOG(R)File 73:EMBASE


05622785 EMBASE No: 1994035282
Granulocyte colony-stimulating factor induction of improved leukocytopenia with inflammatory flare in a Felty's syndrome patient
Yasuda M.; Kihara T.; Wada T.; Shiokawa S.; Furuta E.; Suenagu Y.; Nonaka

S.; Nobunaga M.; Yoshioka K.; Isayama T.
Medical Institute of Bioregulation, Kyushu University,Beppu Japan
Arthritis and Rheumatism ( ARTHRITIS RHEUM. ) (United States) 1994, 37/1 (145-146)
CODEN: ARHEA ISSN: 0004-3591
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH

13/7/29 (Item 16 from file: 73)
DIALOG(R)File 73:EMBASE


05619503 EMBASE No: 1994014905
The current and future therapy strategies of rheumatoid **arthritis** (RA)
GEGENWARTIGE UND ZUKUNFTIGE THERAPIESTRATEGIEN DER RHEUMATOIDEN **ARTHRITIS** (RA)
Schacht E.
Hauptabteilung Med. Wissenschaften, E. Tosse und Co. GmbH,
Friedrich-Ebert-Damm 101,22047 Hamburg Germany
Zeitschrift fur Rheumatologie ( Z. RHEUMATOL. ) (Germany) 1993, 52/6 (365-382)
CODEN: ZRHMB ISSN: 0340-1855
DOCUMENT TYPE: Journal; Review
LANGUAGE: GERMAN SUMMARY LANGUAGE: GERMAN; ENGLISH

The triad of inflammation, immunoproliferation and synovial hyperplasiais recognized in the pathogenesis of rheumatoid **arthritis**, however, the sequence of events remains as highly controversial as ever. The 'RA pyramid' was established on the assumption that inflammation is at the top with the destructive processes as sequelae. The moderate successes achieved by conservative therapy with regard to long-term outcome cast doubt on this hypothesis. Inhibitors of prostaglandin synthesis have not been and are not disease modifying. Do substances which influence the endothelial adhesion molecules or leucocyte adhesion receptors (leumedines) promise to be more successful? Do the empirically developed disease modifying antirheumatic drugs (Gold parenteral, MTX) have to be administered earlier? Unfortunately, there is a need for a differential diagnosis which is prognostically valid with regard to the dynamics and aggressiveness of rheumatoid **arthritis**. Moreover, a pharmacological basis for optimally founded combination strategies is also lacking. Presently, the emphasis of research is directed at the regulation of dysfunctional immune systems. Immunosuppressives (cyclosporin A), cytokine antagonists, receptor antagonists and soluble cytokine receptors (IL-1, IL-6, **TNF**-alpha), antibodies against lymphocyte subgroups (CDinf 4, CDinf 7) or against cytokines and their receptors are part of the arsenal for the medium term. Too little is still known about the role of protective cytokines (TGF-beta, IL-4, gamma-INF). Currently, however, it is prognosticated that these targeted therapies will only succeed in RA subgroups or only in intelligent combinations. More attractive alternatives are strategic therapy modalities which intervene very early in the pathological process, such as the modulation of antigen presentation (MHC blocking peptides, T-cell receptor antagonists, T-cell vaccination) or the induction of tolerance against autoantigens through the oral administration of antigens (collagen II, HSP's, OM-8980). If the center of the pathological process, however, is found in the synovial proliferation of tumor-like cell clusters, then there are only a few years at the beginning of the disease when there is a real chance to impede destruction. In this case, aggressive induction therapy can be the only key to success. In the future, specifically active cytostatics (inhibitors of angiogenesis) will have to be developed and clinical trials conducted on adjuvant therapies with substances which strengthen bone and cartilage, making them more resistant to aggressive cell clusters (bisphosphonates, calcitonins, metalloproteinase- or

collagenase-inhibitors).

13/7/30 (Item 17 from file: 73)
DIALOG(R)File 73:EMBASE


05607492 EMBASE No: 1994010190
Eosinophilia-myalgia syndrome, toxic-oil syndrome, and diffuse fasciitis with eosinophilia
Silver R.M.
Division of Rheumatology/Immunology, Department of Medicine, Medical University of South Carolina, 171 Ashley Avenue,Charleston, SC 29425 United States
Current Opinion in Rheumatology ( CURR. OPIN. RHEUMATOL. ) (United States ) 1993, 5/6 (802-808)
CODEN: CORHE ISSN: 1040-8711
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

13/7/31 (Item 18 from file: 73)
DIALOG(R)File 73:EMBASE


05607477 EMBASE No: 1994010175
Myositis and myopathies: Editorial overview
Kagen L.J.
Department of Medicine, Hospital for Special Surgery, 535 East 70th Street,New York, NY 10021 United States
Current Opinion in Rheumatology ( CURR. OPIN. RHEUMATOL. ) (United States ) 1993, 5/6 (691-694)
CODEN: CORHE ISSN: 1040-8711
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH

13/7/32 (Item 19 from file: 73)
DIALOG(R)File 73:EMBASE


05565682 EMBASE No: 1993333782
Graft-versus-host disease: Host and donor views
Deeg H.J.; Yolken; Rostami; Nelson; Pahwa; Schaffer; Boxer
Fred Hutchinson Cancer Research Ctr., 1124 Columbia St,Seattle, WA 98104 United States
Seminars in Hematology ( SEMIN. HEMATOL. ) (United States) 1993, 30/4 SUPPL. 4 (110-118)
CODEN: SEHEA ISSN: 0037-1963
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Major histocompatibility complex (MHC) antigens, termed HLA in man, provide the major barrier to transplantation. Clinical manifestations of the host-versus-graft reaction are generally referred to as rejection and those of the graft-versus-host (GVH) reaction as graft-versus-host disease (GVHD). GVHD can occur after transplantation of marrow or solid organs or t ransfusion of blood products. GVHD involves antigen-presenting cells, which are recognized by T lymphocytes via the T-cell receptor. CD4 and CD8 serve as accessory molecules. This interaction results in T-cell activation, expression of interleukin-2 receptors (IL-2R) and the production of IL-2 followed, generally, by clonal proliferation and differentiation associated with lymphokine secretion and dysregulation that may involve interferon-gamma; **tumor necrosis** factor-alpha: IL-2, -3, -4, -5, -6, and

-9; granulocyte macrophage colony-stimulating factor (GM-CSF); and other factors. Effector cells such as cytotoxic T cells, natural killer (NK) cells, and macrophages become activated, mostly by bone marrow-derived lymphohemopoietic cells, and contribute to cell and tissue death. Many of the cytokines also alter vascular endothelium; conceivably these changes also affect homing of cells and allogeneic interactions. Another factor is the administration of in vivo GVHD prophylaxis, which may modify both undesirable (GVHD-inducing) and desirable (tolerance-inducing) mechanisms. Exogenous hematopoietic growth factors and cytokines recently introduced into clinical trials may interfere with endogenous feedback loops in a positive or negative fashion. Adverse reactions have been observed with IL-2 and with interferon. Potentially beneficial effects have been reported with the use of soluble IL-1R or IL- 1R-antagonist. A better understanding of the interactions between donor and host components might lead to regimens that modify not only the donor marrow (eg, T cells), but also the host environment such that alloreactions can be controlled and tolerance established.

13/7/33 (Item 20 from file: 73)
DIALOG(R)File 73:EMBASE


05521168 EMBASE No: 1993289267
Interleukin-1 receptor antagonist
Arend W.P.
Division of Rheumatology, Department of Medicine, Colorado Univ. Health Sciences Ctr.,Denver, CO 80262 United States
Advances in Immunology ( ADV. IMMUNOL. ) (United States) 1993, 54/- (167-227)
CODEN: ADIMA ISSN: 0065-2776
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

IL-1ra is the first described naturally occurring receptor antagonist of any cytokine or hormone-like molecule. IL-1ra is a member of the IL-1 family by three criteria: amino acid sequence homology of 26 to 30% to IL-1beta and 19% to IL-1alpha; similarities in gene structure; and common gene localization to human chromosome 2q14. Two structural variants of IL-1ra exist: sIL-1ra, a secretory molecule produced by monocytes, macrophages, neutrophils, fibroblasts, and other cells; and icIL-1ra, an intracellular molecule produced by keratinocytes and other epithelial cells, macrophages, and fibroblasts. IL-1ra production by monocytes, macrophages, and neutrophils may be regulated in a differential fashion with IL-1beta. Human IL-1ra binds to both human IL-1RIs and IL-1RIIs on cell surfaces, although with 100-fold greater avidity to IL-1RIs. IL-1ra may bind preferentially to soluble IL- 1RIs and not at all to soluble IL-1RIIs. IL-1ra competitively inhibits binding of both IL-1alpha and IL-1beta to cell surface receptors without inducing any discernible intracellular responses. All three forms of IL-1 may bind to IL-1 receptors in a similar fashion but IL-1ra may lack the secondary interactions necessary to trigger cell responses. A 100-fold or greater excess of IL-1ra over IL-1 may be necessary to inhibit biological responses to IL-1 both in vitro and in vivo. The roles of sIL-1ra and icIL-1ra in normal physiology or in host defense mechanisms remain unclear. The administration of IL-1ra blocks the effects of IL-1 in some animal models of septic shock, inflammatory **arthritis**, graft-versus-host disease, and inflammatory bowel disease. The preliminary results of clinical trials in humans indicate possible efficacy of IL-1ra in sepsis syndrome, rheumatoid **arthritis**, and GVHD.

13/7/34 (Item 21 from file: 73)
DIALOG(R)File 73:EMBASE

05516131 EMBASE No: 1993284230
Future aspects of new therapeutic possibilities of rheumatic diseases
NEUE THERAPEUTISCHE MOGLICHKEITEN. ZUKUNFTSASPEKTE
Rubbert A.; Burmester G.-R.
Inst. fur Klin. Immunol./Rheumatol., Medizinische Klinik III, Universitat Erlangen-Nurnberg, Krankenhausstrasse 12,D-91054 Erlangen Germany
Internist ( INTERNIST ) (Germany) 1993, 34/9 (841-851)
CODEN: INTEA ISSN: 0020-9554
DOCUMENT TYPE: Journal; Review
LANGUAGE: GERMAN SUMMARY LANGUAGE: GERMAN

13/7/35 (Item 22 from file: 73)
DIALOG(R)File 73:EMBASE


05450048 EMBASE No: 1993218147
Synovial mononuclear phagocytes in rheumatoid **arthritis** and osteoarthritis: Quantitative and functional aspects
Weinberg J.B.; Wortham T.S.; Misukonis M.A.; Patton K.L.; Chitneni S.R.
Duke University Medical Center, 508 Fulton Street,Durham, NC 27705 United States
Immunological Investigations ( IMMUNOL. INVEST. ) (United States) 1993, 22/5 (365-374)
CODEN: IMINE ISSN: 0882-0139
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Macrophages are normal constituents of synovial tissue, and in inflammatory synovitis the number of synovial macrophages increases. Synovial macrophages and their secretory products are important in initiating, propagating, and maintaining the synovial inflammation in rheumatoid **arthritis** (RA). The purpose of this study was to determine the absolute numbers of macrophages in synovia resected from patients with RA and osteoarthritis (OA) and to determine their abilities to produce and/or functionally express **tumor necrosis** factor (**TNF**), interleukin-1 (IL-1), and tissue factor (thromboplastin). Results demonstrate that synovial tissue from RA patients (as compared to that from OA patients) weighed more, contained more cells, more macrophages, and more multinucleated giant cells (macrophage polykaryons). Also, isolated cells from both OA and RA patients had tissue factor activity, and could produce **TNF** and IL-1 with in vitro culture, but these parameters were not different in cells from OA and RA patients. RA patients receiving glucocorticoid treatment for their **arthritis** had fewer total synovial cells than did patients not on glucocorticoids, but treatment with nonsteroidal anti-inflammatory agents did not alter cell numbers. Patient treatment with glucocorticoids or non-steroidal anti-inflammatory drugs did not influence the ability of their isolated cells to produce **TNF** or IL-1.

13/7/36 (Item 23 from file: 73)
DIALOG(R)File 73:EMBASE


05407723 EMBASE No: 1993175822
Rheumatoid **arthritis**: New science, new treatment
Miller-Blair D.J.; Robbins D.L.
Kaiser-Permanente Medical Center,South Sacramento, CA United States
Geriatrics ( GERIATRICS ) (United States) 1993, 48/6 (28-38)
CODEN: GERIA ISSN: 0016-867X
DOCUMENT TYPE: Journal; Review

LANGUAGE: ENGLISH  SUMMARY LANGUAGE: ENGLISH

Rheumatoid **arthritis** (RA) is a chronic systemic inflammatory disease that occurs two to four times as often in women as in men and increases in incidence with advancing age. It affects synovial-lined joints and can also affect the pulmonary, cardiac, nervous, integumentary, and reticuloendothelial systems. RA is manifested clinically by malaise and fatigue, followed by a symmetric pattern of joint inflammation characterized by pain and stiffness. RA most likely occurs in the setting of a genetically predisposed individual, triggered by infectious agents or endogenous antigens. Many of the newer treatments being studied involve blocking cytokine-mediated interactions between cells of the synovium.

13/7/37  (Item 24 from file: 73)
DIALOG(R)File 73:EMBASE


05367642  EMBASE No: 1993135727
Therapeutic applications of photopheresis
Rook A.H.; Cohen J.H.; Lessin S.R.; Vowels B.R.
Department of Dermatology, Hospital University of Pennsylvania, 3400 Spruce Street,Philadelphia, PA 19104 United States
Dermatologic Clinics ( DERMATOL. CLIN. ) (United States) 1993, 11/2 (339-347)
CODEN: DRMCD  ISSN: 0733-8635
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH  SUMMARY LANGUAGE: ENGLISH

Photopheresis is a useful therapy for advanced cutaneous T-cell lymphoma/particularly for Sezary syndrome. Additional conditions in which clinical studies have suggested a therapeutic role for photopheresis include certain **autoimmune** diseases and reversal of rejection of solid organ allografts. Because photopheresis is extremely well tolerated and evidence is lacking for a direct immunosuppressive effect produced by this therapy, randomized trials should be pursued to determine the full spectrum of clinical benefit of this novel therapeutic modality.

13/7/38  (Item 25 from file: 73)
DIALOG(R)File 73:EMBASE


05341933  EMBASE No: 1993110018
CME examination
Annals of Allergy ( ANN. ALLERGY ) (United States) 1993, 70/4 (274-275)
CODEN: ANAEA  ISSN: 0003-4738
DOCUMENT TYPE: Journal; Note
LANGUAGE: ENGLISH

13/7/39  (Item 26 from file: 73)
DIALOG(R)File 73:EMBASE


05341932  EMBASE No: 1993110017
Immunosuppressive therapy for **autoimmune** diseases
Hoffman G.S.
Cleveland Clinic Foundation, 9500 Euclid Ave,Cleveland, OH 44195 United States
Annals of Allergy ( ANN. ALLERGY ) (United States) 1993, 70/4 (263-274)
CODEN: ANAEA  ISSN: 0003-4738
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH

13/7/40 (Item 27 from file: 73)
DIALOG(R)File 73:EMBASE


05266008 EMBASE No: 1993034093
Wegener's granulomatosis
Hoffman G.S.
Rheumatic/Immunologic Diseases Dept., Cleveland Clinic Foundation, 9500 Euclid Avenue,Cleveland, OH 44195 United States
Current Opinion in Rheumatology ( CURR. OPIN. RHEUMATOL. ) (United States ) 1993, 5/1 (11-17)
CODEN: CORHE ISSN: 1040-8711
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

In recent years, interest in Wegener's granulomatosis has been stimulated by an increasing appreciation of the chronic relapsing nature of this disease and its association with antibodies to proteinase 3. Although conventional therapy with cyclophosphamide and glucocorticoids has produced remission in most patients, remission may not occur immediately and, in at least 50% of patients, may be followed by relapse. As a result, most patients experience some form of permanent morbidity from disease or treatment, or both. These observations have led to renewed efforts to identify more effective and less toxic therapies. Preliminary studies have evaluated other cytotoxic agents, such as **methotrexate**, and biologic products, such as high-dose immunoglobulin and monoclonal antibodies. It is hoped that a better understanding of the possible pathogenic role of anti-proteinase 3 antibodies may contribute to improved therapy. Unfortunately, research is handicapped by lack of an animal model, without which it will be difficult to prove convincingly that anti-proteinase 3 antibodies are important in expressing disease.

13/7/41 (Item 28 from file: 73)
DIALOG(R)File 73:EMBASE


05215370 EMBASE No: 1992355604
Use of monoclonal antibodies in vivo as a therapeutic strategy for alloimmune or **autoimmune** reactivity: The Besancon experience
Herve P.; Racadot E.; Wendling D.; Rumbach L.; Tiberghien P.; Cahn J.Y.; Flesch M.; Wijdenes J.
Centre Reg. de Transfusion Sanguine, 1 Boulevard Fleming,25020 Besancon France
Immunological Reviews ( IMMUNOL. REV. ) (Denmark) 1992, -/129 (31-55)
CODEN: IMRED ISSN: 0105-2896
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH

13/7/42 (Item 29 from file: 73)
DIALOG(R)File 73:EMBASE


05157035 EMBASE No: 1992297268
Is there a disease-modifying drug for juvenile chronic **arthritis**?
Rooney M.
Molecular Rheumatology Section, MRC Clinical Research Centre, Watford Road,Harrow, Middlesex HA1 3UJ United Kingdom
British Journal of Rheumatology ( BR. J. RHEUMATOL. ) (United Kingdom) 1992, 31/9 (635-641)
CODEN: BJRHD ISSN: 0263-7103

DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH

13/7/43 (Item 30 from file: 73)
DIALOG(R)File 73:EMBASE
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05078093 EMBASE No: 1992218309
Profile of cytokines in synovial fluid specimens from patients with **arthritis**. Interleukin 8 (IL-8) and IL-6 correlate with inflammatory arthritides
Remick D.G.; DeForge L.E.; Sullivan J.F.; Showell H.J.
I301 Catherine Road,Ann Arbor, MI 48109-0602 United States
Immunological Investigations ( IMMUNOL. INVEST. ) (United States) 1992, 21/4 (321-327)
CODEN: IMINE ISSN: 0882-0139
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The synovial fluid aspirated from patients with symptomatic **arthritis** was analyzed for the presence of **tumor necrosis** factor (**TNF**), interleukin 6 (IL- 6) and interleukin 8 (IL-8). All three cytokines were found in both inflammatory and non-inflammatory arthritides: IL-8 levels ranged from less than 20 to 38,990 pg/ml, IL-6 from less than 10 to 72,300 pg/ml and **TNF** from less than 4 to 61 pg/ml. No inhibitors of cytokine activity were found. IL-8 and IL-6 were present in significantly higher levels in patients with inflammatory **arthritis** compared to patients with osteoarthritis, and there was significant correlation between the IL-6 and IL-8 levels. These findings document the presence of multiple cytokines in the synovial fluid specimens of patients with **arthritis**, and demonstrate that higher cytokine levels accompany inflammatory **arthritis**.

13/7/44 (Item 31 from file: 73)
DIALOG(R)File 73:EMBASE
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04898958 EMBASE No: 1992039173
Angiogenesis and its inhibition: Potential new therapies in oncology and non-neoplastic diseases
Billington D.C.
Institut de Recherches Servier, 11 Rue des Moulineaux, 92150 Suresnes France
Drug Design and Discovery ( DRUG DES. DISCOV. ) (United Kingdom) 1991, 8/1 (3-35)
CODEN: DDDIE ISSN: 1055-9612
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The ability to mount an angiogenic response is probably present in all tissues, and stimulation of endothelial cells by any one of a wide variety of factors initiates a cascade of events leading to angiogenesis. In most tissues the overall lack of angiogenesis in normal situations probably results from the interaction of a complex series of multifactorial systems, each of which maintained in a state of balance between stimulation and inhibition. An imbalance in any one these systems, for example by an increase in the concentration of a growth factor, may lead to angiogenesis. Inhibition of angiogenic stimuli is unlikely to be effective as an approach to new angiostatic drugs, given the multiple stimulatory pathways available. Tumour cells for example may induce angiogenesis via release of nuemerous growth factors, prostaglandins ect, and by their attraction of inflammatory cells which in turn release multiple angiogenic stimuli.

Inhibitory modulation of many of the individual steps of capillary growth which occur following an angiogenic stimulus can block the angiogenic response. This leads to the expectation that an effective inhibitor of a single key step in this cascade would be able to completely suppress angiogenesis. Inappropriate angiogenesis is an important factor in many disease including cancer and **arthritis**. In particular angiogenesis is an absolute requirement for neoplastic growth of solid tumours, and the establishment of secondary growths. There is also a strong link between induction of angiogenesis by a tumour and its ability to metastasise.

13/7/45 (Item 32 from file: 73)
DIALOG(R)File 73:EMBASE


04880834 EMBASE No: 1992021049
Cytokines and drugs workshop
Hom J.T.; Simon P.L.
Lilly Research Laboratories,Indianapolis IN 46285 United States
Agents and Actions ( AGENTS ACTIONS ) (Switzerland) 1991, 35/SUPPL. (147-150)
CODEN: AGACB ISSN: 0065-4299
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH

13/7/46 (Item 33 from file: 73)
DIALOG(R)File 73:EMBASE


04880603 EMBASE No: 1992020818
Interaction(s) between essential fatty acids, eicosanoids, cytokines, growth factors and free radicals: Relevance to new therapeutic strategies in rheumatoid **arthritis** and other collagen vascular diseases
Das U.N.
Department of Medicine, Nizam's Institute, of Medical Sciences,Hyderabad 500482 India
Prostaglandins Leukotrienes and Essential Fatty Acids ( PROSTAGLANDINS LEUKOTRIENES ESSENT. FATTY ACIDS ) (United Kingdom) 1991, 44/4 (201-210)
CODEN: PLEAE ISSN: 0952-3278
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Eicosanoids, lymphokines, and free radicals are known to participate in the pathogenesis of inflammation. **Tumour necrosis** factor ( **TNF**), interleukin-1 and 6 (IL-1 and IL-6) and colony stimulating factor-1 (CSF-1) are secreted mainly by activated macrophages, whereas T-cells secrete IL-2, IL-3, IL-4 and interferon-gamma (IFN-gamma). In addition, activated macrophages and lymphocytes can also produce eicosanoids and free radicals which have potent pro-inflammatory actions. Eicosanoids, lymphokines, and free radicals can modulate the immune response, cell proliferation, stimulate collagenase and proteases secretion and induce bone resorption; events which are known to be associated with various collagen vascular diseases. On the other hand transforming growth factor-beta (TGF-beta) produced by synovial tissue, platelets and lymphocytes can inhibit collagenase production, suppress T-cell and NK-cell proliferation and activation and block free radical generation and seems to be of benefit in rheumatoid **arthritis**. Drugs such as cyclosporine, 1,25,dihydroxycholecalciferol and pentoxyfylline can block lymphokine and **TNF** production and thus, may inhibit the inflammatory process. Essential fatty acids, the precursors of eicosanoids, are suppressors of T-cell proliferation, IL-1, IL-2 and **TNF** production and have been shown to be of benefit in rheumatoid **arthritis**, systemic lupus erythematosus and glomerulonephritis. Thus, the interactions between

essential fatty acids, eicosanoids, lymphokines, TGF-beta and free radicals suggest that new therapeutic strategies can be devised to modify the course of collagen vascular diseases.

13/7/47 (Item 34 from file: 73)
DIALOG(R)File 73:EMBASE


04660801 EMBASE No: 1991154846
Synovial angiogenesis
Liote F.
Clinique de Rhumatologie, Centre Viggo Petersen, 6, Rue Guy-Patin, 75010 Paris France
Revue du Rhumatisme et des Maladies Osteo-Articulaires ( REV. RHUM. MAL. OSTEO-ARTICUL. ) (France) 1991, 58/3 BIS (51-59S)
CODEN: RRMOA ISSN: 0035-2659
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: FRENCH SUMMARY LANGUAGE: ENGLISH

Synovial angiogenesis, the formation of new capillaries from pre-existent capillaries, is a constant feature of synovial inflammation. Strictly regulated, it normally disappears after recovery from the acute episode. However it may persist during chronic synovial inflammation and then participates in pannus development in RA. This is the result of biochemical events which have contributed to breakdown of the extracellular matrix and cartilage in association with activation or secretion into this micro-environment of angiogenic factors. Relations with immuno-competent cells (lymphocytes and monocytes) suggest that this final common pathway may be partially dependent upon stimulation by the antigen. The development of treatment aimed at inhibiting angiogenesis could offer additional therapeutic hope in rheumatoid **arthritis**.

13/7/48 (Item 35 from file: 73)
DIALOG(R)File 73:EMBASE


04642961 EMBASE No: 1991137004
Osteoporosis associated with rheumatoid **arthritis**: Pathogenesis and management
Joffe I.; Epstein S.
Endocrinology/Metabolism Div., Albert Einstein Medical Center, 5401 Old York Rd,Philadelphia, PA 19141 United States
Seminars in Arthritis and Rheumatism ( SEMIN. ARTHRITIS RHEUM. ) (United States) 1991, 20/4 (256-272)
CODEN: SAHRB ISSN: 0049-0172
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Rheumatoid **arthritis** is associated with both localized and generalized osteoporosis. Localized osteoporosis can be considered to be caused by local disease mechanisms, including the generation of factors from activation of the cytokine pathway. The etiology of generalized osteoporosis has been difficult to elucidate, particularly because of the lack of sensitive techniques to measure bone mineral density. The introduction of single- and dual-photon absorptiometry and quantitative computed tomography has allowed more accurate assessment of bone mineral density. In general, bone mineral density loss at appendicular sites does not correlate well with axial bone density loss. Corticosteroid treatment exaggerates the development of osteoporosis in up to 40% of patients with rheumatoid **arthritis**. Sex hormone status, physical activity, disease duration, and functional class are all significant predictors for the development of osteoporosis. Current therapy for prevention and treatment

is based largely on theoretical considerations. Physical activity should be encouraged once acute joint inflammation has settled. Postmenopausal women and amenorrheic premenopausal women will benefit from cyclical estrogen replacement. Patients with low serum 1,25-dihydroxy vitamin Dinf 3 levels, and males with low serum testosterone levels, are candidates for replacement therapy with the appropriate hormones. In patients who are receiving corticosteroids the dose should be limited, and oral calcium supplements are of benefit. The use of the newer corticosteroid deflazacort, and disease-modifying immunosuppressive drugs, are discussed. Other therapeutic options which should be considered, although published trials are scarce, are calcitonin and the diphosphonates. Further studies are awaited concerning the optimum prevention and treatment of osteoporosis associated with rheumatoid **arthritis**. For the present, management should be based on theoretical considerations. The introduction of dual-energy X-ray absorptiometry for measuring bone mineral density represents a significant improvement over the older techniques, and will assist in future clinical trials. Inhibitors of the cytokine pathway, or the products stemming from activation of this pathway, need to be evaluated in the treatment of osteoporosis associated with rheumatoid **arthritis**
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13/7/49 (Item 36 from file: 73)
DIALOG(R)File 73:EMBASE


04577560 EMBASE No: 1991071603
The effects of some anti-arthritic drugs and cytokines on the shape and function of rodent macrophages
Haynes D.R.; Whitehouse M.W.; Vernon-Roberts B.
Department of Pathology, University of Adelaide, GPO Box 498,Adelaide, SA 5001 Australia
International Journal of Experimental Pathology ( INT. J. EXP. PATHOL. ) (United Kingdom) 1991, 72/1 (9-22)
CODEN: IJEPE ISSN: 0959-9673
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Non-steroidal antiinflammatory drugs (NSAID) enhanced the spreading of mouse and rat peritoneal macrophages attached to either plastic or glass. This was probably due to drug inhibition of prostaglandin Einf 2 (PGEinf 2) production since spreading was also inhibited by adding exogenous PGEinf 2. Corticosteroids (dexamethasone, cortisol and prednisolone) and some immunosuppressants (6-mercaptopurine, **methotrexate**, but not cyclosporin-A) also enhanced in-vitro spreading of murine peritoneal macrophages. Some recombinant cytokines (human **tumour necrosis** factor alpha and beta, murine **tumour necrosis** factor alpha, and murine interferon gamma, but not human interferon gamma) also enhanced the spreading of mouse peritoneal macrophages in vitro. Scanning electron microscopy revealed significant differences in morphology of cells induced to spread by these drugs and cytokines. NSAID treatment also enhanced macrophage clumping in vitro, indicating that cell spreading may play an important role in the resolution of inflammatory processes and/or the formation of multinucleated giant cells.

13/7/50 (Item 37 from file: 73)
DIALOG(R)File 73:EMBASE


04469733 EMBASE No: 1990357842
Development of angiogenesis inhibitors for clinical applications
Maione T.E.; Sharpe R.J.
Repligen Corporation, One Kendall Square, Cambridge, MA 02139 United

States
Trends in Pharmacological Sciences ( TRENDS PHARMACOL. SCI. ) (United Kingdom) 1990, 11/11 (457-461)
CODEN: TPHSD ISSN: 0165-6147
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Angiogenesis, the development of new blood vessels, is associated with many life-threatening pathologies. The neovascularization of tumors for example, allows a blood supply to deliver the required nutrients for tumor development. Inappropriate blood vessel growth also contributes to the pathology of other disease such as atherosclerosis and **arthritis**. The process of angiogenesis is beginning to be better understood, and as Ted Maione and Richard Sharpe explain, this understanding has led to the identification of several lead compounds that inhibit this process. At present all of these candidate drugs exhibit severe host toxicity, but more selective angiogenesis inhibitors might be expected to be extremely useful therapeutic agents.

13/7/51 (Item 38 from file: 73)
DIALOG(R)File 73:EMBASE


03034527 EMBASE No: 1985228043
Histologic evaluation of necrosis in osteosarcoma induced by chemotherapy. Regional mapping of viable and nonviable tumor
Picci P.; Bacci G.; Campanacci M.; et al.
Centro Tumori Ossei, Istituto Ortopedico Rizzoli, 40136 Bologna Italy
Cancer ( CANCER ) (United States) 1985, 56/7 (1515-1521)
CODEN: CANCA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

The predominant sites of viable and nonviable tumor were determined in the primary lesions of 50 patients with osteosarcoma after initial treatment with preoperative chemotherapy. The degree of tumor destruction was classified as good, fair, and poor and a map of the sites revealing viable and nonviable tumor was constructed. The study revealed several preferential sites where viable tumor was likely to persist: soft tissues, cortex, subcortex, ligaments, and areas in contact with cartilage (growth plate and/or articular cartilage). Localized areas of hemorrhage and necrosis, designated 'lacunae', were noted within the tumor. They were frequently surrounded by bundles of viable tumor and appeared to correlate with open surgical biopsies. Factors responsible for this phenomenon and the persistence of viable tumors are discussed. The findings have important implications in the design of surgical treatment and in the use of needle biopsies to determine the effects of preoperative treatment.

13/7/52 (Item 39 from file: 73)
DIALOG(R)File 73:EMBASE


02649914 EMBASE No: 1984168872
Preoperative administration of high-dose **methotrexate** for osteosarcoma
Chan K.W.; Knowling M.A.; Duncan C.P.; Morton K.S.
Department of Pediatrics, University of British Columbia, Vancouver, BC V6H 3V4 Canada
Canadian Journal of Surgery ( CAN. J. SURG. ) (Canada) 1984, 27/3 (305-307+309+311)
CODEN: CJSUA
DOCUMENT TYPE: Journal

LANGUAGE: ENGLISH SUMMARY LANGUAGE: FRENCH

13/7/53 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)


07764235 93219728 PMID: 8465132
[If I had chronic polyarthritis--current ideas on basic therapy]
Wenn ich eine chronische Polyarthritis hatte--Neue Ideen zur Basistherapie.
Hasler F
FMH Innere Medizin, speziell Rheumaerkrankungen, Chur.
Schweizerische Rundschau fur Medizin Praxis = Revue suisse de medecine Praxis (SWITZERLAND) Mar 23 **1993**, 82 (12) p349-52, ISSN 1013-2058 Journal Code: 8403202
Document type: Journal Article ; English Abstract
Languages: GERMAN
Main Citation Owner: NLM
Record type: Completed
Rheumatoid **arthritis** (RA) is a chronic inflammatory disorder of largely unknown etiology and complex multifactorial pathogenesis. To date, the medical management has been less than optimal and has consisted primarily of drugs that modulate the acute inflammatory process. Over the years a treatment program referred to as the classical therapeutic pyramid has evolved. A new concept and a controversial one in therapy of RA is that already at the time of definitive diagnosis, a more concerted effort towards vigorous treatment using second-line drugs such as **methotrexate** , should be made. It is very likely that over the next 5 years interventions such as monoclonal antibodies directed against predetermined T-cell subpopulations and anti-cytokines such as **TNF** -alpha binding proteins will evolve as new concepts in therapy of RA.
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13/7/54 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)


120200274 CA: 120(16)200274a JOURNAL
Effect of liposomally encapsulated MTX-DMPE conjugates upon TNF.alpha. and PGE2 release by lipopolysaccharide stimulated rat peritoneal macrophages
AUTHOR(S): Williams, Anwen S.; Topley, N.; Williams, B. D.
LOCATION: Rheumatology Research Laboratory, University of Wales College of Medicine, Heath Park, Cardiff, UK, CF4 4XN
JOURNAL: Biochim. Biophys. Acta DATE: 1994 VOLUME: 1225 NUMBER: 2
PAGES: 217-22 CODEN: BBACAQ ISSN: 0006-3002 LANGUAGE: English
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CA215XXX Immunochemistry
IDENTIFIERS: liposome methotrexate dimyristoylphosphatidylethanolamine conjugate, tumor necrosis factor methotrexate liposome, prostaglandin E2 methotrexate liposome, lipopolysaccharide peritoneum macrophage methotrexate liposome
DESCRIPTORS:
Arthritis,rheumatoid...